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RECURRENT LYMPHOCYTIC CHORIOMENINGITIS

REPORT OF A CASE IN WHICH TREATMENT WAS WITH POOLED NORMAL ADULT SERUM

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The following case is reported because it included many unusual clinical manifestations and is the first case of lymphocytic choriomeningitis to our knowledge in which an attempt was made to treat the disease with pooled normal adult serum.

REPORT OF CASE

B. D., a 22 year old student nurse, was admitted to Michael Reese Hospital on May 4, 1941. Her past history contained nothing of medical significance except for a "sleeping episode" five years previously, while she was living in El Cajon, San Diego County, Calif. The only additional information obtainable was that the patient had an "unpleasant disposition" at that time, from which she recovered.

The patient had been perfectly well until 10 p. m. on May 4, 1941, when, after taking a long walk and returning to her room, she felt faint, with palpitation and tachycardia. She became apprehensive and then fainted.

Immediate examination revealed the patient to be in apparent deep coma, completely flaccid and unresponsive to stimuli. Her respirations were rapid and shallow. The pulse was rapid, with a rate of 110 to 130 per minute, and the blood pressure was 130 systolic and 80 diastolic. General physical examination gave essentially negative results. The deep reflexes were all present, equal and hyperactive, and there were no pathologic reflexes. During the succeeding several hours the patient was roused from her stupor for periods of a few moments, but she appeared dazed and only at times seemed lucid. She could be awakened by a very loud noise or a painful stimulus, after which her attention could be sustained by conversation.

The following morning the patient could be aroused and had less difficulty remaining awake. She appeared rational in her responses but was not alert. On the evening of May 6, the patient again became deeply stuporous and could not be aroused during the night. The following morning she could again be aroused, although she remained apathetic and indifferent. On the morning of May 7, while she was being examined, weakness suddenly developed in the right lower two thirds of the face, the right arm and the right leg. There was no spontaneous movement on the right side. The reflexes of the right arm were diminished; the abdominal reflexes were absent on the right side, and there were positive Babinski, Gordon and Oppenheim signs on the right. The Beevor sign was positive to the left. The Hoover sign was typical of organic weakness of the right leg. There was complete hemianesthesia to touch, pain, temperature, pressure and position of the right side of the face and the body, anteriorly and posteriorly, with a midline demarcation. In attempting to walk the patient fell to the right. There was definite ataxia on the right side. Examination of the cranial nerves disclosed a loss of conjugate deviation of the eyes to the right, right homonymous hemianopsia, normal pupillary responses to light but sluggish responses in accommodation, paresis of the right side of the face of the central type, complete middle ear deafness on the

From the Samuel Deutsch Serum Center, Michael Reese Hospital.

This case is reported with the permission of Dr. H. F. Binswanger and Dr. J. Reich, attending physician and neurologic consultant, respectively, of the hospital nurses' service of Michael Reese Hospital.

right side (present since a mastoidectomy on that side six years before), protrusion of the tongue to the left, deviation of the jaw to the left and anesthesia of the right side of the face. A lumbar puncture performed at this time yielded fluid essentially normal (table 1). Other laboratory findings are summarized in table 2. Roentgenograms of the chest and the head were essentially normal.

The following day, slight rigidity of the neck and the back developed, with pain in the neck and down the back on attempted flexion of the neck. The Kernig sign was positive bilaterally.

In the subsequent forty-eight hours, the weakness and neurologic symptoms progressed. Extreme apathy continued. On the morning of May 11, the patient became stuporous and

TABLE 1.—*Findings in the Cerebrospinal Fluid*

Date	5/7/41	5/11/41	6/9/41
Ross-Jones test	Negative	Negative	Negative
Total cells per cubic millimeter	1	2	1
Lymphocytes, per cent	100	100	100
Lange colloidal gold curve	1111100000	0000000000	1111000000
Sugar, mg. per 100 cc.	69	..	69
Chlorides, mg. per 100 cc.	752	..	703
Protein, mg. per 100 cc.	30	..	32
Culture and smear	Negative	Negative	Negative
Wassermann and Kahn tests	Negative	Negative	Negative
Pressure, cm. of fluid	12	6	12
Response to compression of jugular vein	Normal	Normal	Normal

TABLE 2.—*Summary of Laboratory Data*

Date	5/7/41	5/9/41	5/11/41	5/12/41	5/14/41	6/9/41	6/13/41
Blood chemistry	Normal	Normal	—	—	—	—	Normal
Red cell count	Normal	—	Normal	Normal	Normal	Normal	—
White cell count, per cubic millimeter	10,350	—	8,000	28,200	10,700	5,900	—
Differential white cell count, per cent							
Neutrophils	66	—	70	92	73	59	—
Lymphocytes	27	—	25	4	22	28	—
Eosinophils	0	—	0	0	2	6	—
Monocytes	5	—	5	4	3	5	—
Basophils	0	—	0	0	0	2	—
Blood cultures	No growth	—	No growth	—	—	—	No growth
Sedimentation rate	—	—	—	—	—	—	28 mm. per hour
Agglutination tests							
Typhoid	—	—	—	—	—	—	Negative
Paratyphoid A and B	—	—	—	—	—	—	Negative
Brucella abortus	—	—	—	—	—	—	Negative
Brucella melitensis	—	—	—	—	—	—	Negative
Heterophil	—	—	—	—	—	—	1/32
Wassermann and Kahn reactions of blood	Negative	—	—	—	—	—	Negative
Urinalysis	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Examination of stool	Normal	—	—	—	—	—	Normal

unresponsive. The respirations were slow and shallow. In addition to the complete hemianesthesia and hemiplegia, the left extremities were flaccid. No deep reflexes could be elicited in the left arm, but they were present in the left leg. The patient was awakened by firm supraorbital pressure and gave monosyllable responses to questions. There were a definite weakness of the left arm and left leg, pronounced stiffness of the neck and a strongly positive Kernig sign bilaterally, a complete external ophthalmoplegia, absence of pupillary reaction in accommodation, though the response to light was normal, and a gross defect in the left field of vision as well as in the right.

During the day the patient became more stuporous and totally blind, and the respirations dropped to 9 per minute. The patient's condition appeared critical, and she was given 2,000 cc. of a 10 per cent solution of dextrose in distilled water during the afternoon. At 9 p. m. on May 11, she was given 500 cc. of pooled normal adult human serum intravenously in the course of three hours. One-half hour after the serum had been injected, the patient had a chill, during which time her right side moved with the chill. At the same time she became lucid, in marked contrast to her condition previously. Her temperature rose to 102.2 F. after the chill and dropped promptly the following morning.

The following morning, the patient was clear mentally. Sensation was normal throughout; there was improved strength in the right arm and leg, and the abdominal reflexes had returned on the right side. There was a normal plantar response on the right. The external ophthalmoplegia had almost disappeared, and accommodation responses were almost normal. The paralysis of the right side of the face was definitely less, and there was midline protrusion of the tongue. Meningeal signs were less pronounced. An additional 500 cc. of serum was administered. No pyrogenic reaction followed this administration. Rapid improvement continued, and the following morning, thirty-two hours after the first injection of serum, recovery appeared almost complete.

The patient continued to convalesce for the next ten days. There was only a low grade fever, the temperature rising to 99.6 F., from May 17 to 21. Her recovery was not complete, however, because there were a residual slight weakness of the right extremities, noticeable dragging of the right leg and a positive Romberg sign. The patient did not have normal "associated movement" of the right arm on walking, and she became fatigued easily.

For the next ten days the condition remained unchanged. The patient had severe headaches during the latter part of the period and was reluctant to be up and about.

On the morning of June 8, she again was found in a deep sleep. Although she could be easily aroused and was coherent and oriented, she had difficulty in remaining awake. All findings at this time were normal. At 1:15 p. m. her respiratory rate dropped to 4 per minute, with slight cyanosis. The stupor was deep, and she rapidly acquired paresis of the right side of the face, deviation of the tongue to the right on protrusion and diminished abdominal reflexes on the right. She was in a deep stupor and could be aroused at times only by firm supraorbital pressure. She was given 2,000 cc. of a 5 per cent solution of dextrose in saline solution that afternoon. At midnight her coma was deep. Respirations were at a rate of 5 per minute, with occasional deep sighs. The extremities were limp, without response to pinprick. The ocular fundi were normal.

The following morning, the patient awoke spontaneously. At this time the neurologic findings were not as marked as previously. The patient wavered between stupor and semistupor the rest of the day. That evening, with the respiratory rate down to 4 per minute, 500 cc. of pooled normal adult serum was administered. After the administration, the patient again awoke spontaneously, stating that she felt better, although she had a severe headache. This time she appeared alert and lucid, with spontaneous responses and normal reactions. The neurologic examination at this time revealed no abnormality. One hour later the patient had a chill, followed by a slight rise of temperature in about two hours; the temperature returned to normal the following morning. It is significant that there was subjective and objective recovery preceding the elevation of temperature.

The patient's convalescence in the next two and a half weeks was completely uneventful except for a herpes simplex on the upper lip which developed on June 12. At the time of her discharge she was bright and happy; her emotional and personality responses were normal, and recovery appeared to be complete. The patient was in good health when last seen, one and a half years after her illness.

VIRUS STUDIES

Evidence that our stock guinea pigs and albino Swiss mice were free from latent choriomeningitis infection has been presented by one of us (A. M.) in the earlier publications.[1] As previously, rectal thermometers used in taking temperatures of guinea pigs were routinely disinfected in solution of formaldehyde U. S. P. diluted 1 to 10, to prevent possible intrarectal transmission.

Cerebrospinal fluid collected from the patient on May 8, 1941 (four days after the onset of symptoms) was inoculated subcutaneously (1.5 cc.) into 2 normal guinea pigs and intracerebrally (0.03 cc.) into 6 albino Swiss mice. One cubic centimeter of the fluid which was seeded into various aerobic and anaerobic culture mediums and incubated at 37 C. showed no bacteriologic growth in fourteen days. The first guinea pig had fever (temperature 104.7 F.) on the eighth day after inoculation and was killed on the thirteenth day, when moribund. The second guinea pig's temperature rose to 104.2 F. on the tenth day, and it was found dead on the sixteenth day. At necropsy the brains of both animals were grossly congested, and areas of interstitial bronchopneumonia were seen in stained sections of the lungs. No bacteria were isolated from the brain tissues or heart blood of either guinea pig.

1. (*a*) Milzer, A.: Studies on the Transmission of Lymphocytic Choriomeningitis Virus by Arthropods, J. Infect. Dis. **70**:152-172 (March-April) 1942. (*b*) Milzer, A., and Levinson, S. O.: Laboratory Infection with the Virus of Lymphocytic Choriomeningitis: A Two Year Study of Antibody Response, J. A. M. A. **120**:27-30 (Sept. 5) 1942.

All of the 6 inoculated mice had rough coats, tremors and tonic convulsions typical of lymphocytic choriomeningitis [2] in seven to nine days after inoculation. Two mice died on the eighth day, while the rest recovered and were subsequently immune to challenge intracerebral inoculation of 1,000 minimal lethal doses of the J. P. strain [3] of choriomeningitis virus.

Virus recovered from each guinea pig was subsequently identified as that of lymphocytic choriomeningitis by means of a neutralization test with human choriomeningitis convalescent serum. The technic of the neutralization test used has been described in an earlier paper.[1a] Positive controls consisting of known virus plus immune serum and negative controls consisting of virus plus normal serum were included in all neutralization tests.

The second specimen of cerebrospinal fluid collected from the patient during the recrudescence on June 8 (thirty-four days after the initial attack) was inoculated subcutaneously (1 cc.) into 2 guinea pigs and intracerebrally (0.03 cc.) into 4 albino Swiss mice. No bacteria were isolated from the spinal fluid. One guinea pig had pyrexia (temperature, 104.6 F.) on the tenth day following inoculation and was killed five days later, when moribund. The second guinea pig had a temperature of 105 F. on the eleventh day and was killed, when moribund, on the sixteenth day. Pathologic changes in the brain and lungs of both animals were typical of lymphocytic choriomeningitis.[4] The animals' brain tissues and heart blood were bacterially sterile, and virus recovered from each guinea pig was positively identified by neutralization tests. The inoculated mice had rough coats and tremors seven to ten days after inoculation but recovered and subsequently resisted intracerebral inoculation of 1,000 minimal lethal doses of the J. P. strain of choriomeningitis virus.

After being maintained by subcutaneous inoculation in guinea pigs for ten passages, the new strains were titrated for infectivity. It was found that the first strain isolated (D-1) would consistently kill guinea pigs when 0.5 cc. of a 10^{-4} dilution in buffered solution of sodium chloride was inoculated subcutaneously. On the other hand, the second strain isolated (D-2) seemed to be more pathogenic, because it killed in 10^{-6} dilutions.

Further studies showed that there was complete cross immunity between the newly isolated strains from the patient and the J. P., A. M.[1b] and W. E. (Rivers) strains, proved by resistance to 1,000 minimal lethal doses of virus given intracerebrally in albino Swiss mice which had been infected and had recovered. Histologic examination of stained sections of the brains of guinea pigs and white mice that succumbed to the new strains revealed round cell infiltration of the meninges and choroid plexus identical with that produced by the W. E. (Rivers) [2] and J. P. strains of virus.[3] Filtration experiments have shown that the new strains suspended in nutrient broth of p_H 7.2 (5 per cent brain tissue suspension) readily pass through Berkefeld N and W candles at a negative pressure of 35 cm. of mercury.

IMMUNOLOGIC STUDIES ON THE PATIENT'S BLOOD SERUM

Serum collected from the patient on August 5 (eighty-seven days after the onset of symptoms) failed to neutralize the newly isolated and J. P. strains of virus. The complement-fixing antibody titer was 1/40 (serum dilution), with a saline extract of pooled infected guinea pig spleens used as the antigen.[5] Known positive and negative controls were included in complement fixation as well as neutralization tests.

Five months (October 8) after the onset of the disease the patient's serum showed slight protection against the isolated and J. P. strains. The complement-fixing antibody titer was 1/80. In other tests the serum failed to neutralize the B. A. I. strain of the western type of equine encephalomyelitis virus,[6] but showed strong neutralization of the D.219 strain of St. Louis encephalitis virus.[7] Howitt's technic [8] was followed in the protection tests with the equine encephalomyelitis and St. Louis encephalitis viruses.

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2. Rivers, T. M., and Scott, T. F. McN.: Meningitis in Man Caused by a Filterable Virus: II. Identification of the Etiologic Agent, J. Exper. Med. **63**:415-432 (March) 1936.

3. Leichenger, H.; Milzer, A., and Lack, H.: Recurrent Lymphocytic Choriomeningitis Treated with Sulfanilamide: Isolation of Virus, J. A. M. A. **115**:436-440 (Aug. 10) 1940.

4. Findlay, G. M., and Stern, R. O.: Pathological Changes Due to Infection with the Virus of Lymphocytic Choriomeningitis, J. Path. & Bact. **43**:327-338, 1936. Rivers and Scott.[2]

5. Smadel, J. E.; Baird, R. D., and Wall, M. J.: Complement-Fixation in Infections with the Virus of Lymphocytic Choriomeningitis, Proc. Soc. Exper. Biol. & Med. **40**:71-73 (Jan.) 1939. Smadel, J. E.; Wall, M. J., and Baird, R. D.: A Soluble Antigen of Lymphocytic Choriomeningitis: II. Characteristics of the Antigen and Its Use in Precipitin Reactions, J. Exper. Med. **71**:43-53 (Jan.) 1940.

6. Obtained through Dr. Joseph Zichis, of the Illinois Department of Public Health.

On Jan. 1, 1942 (two hundred and thirty-two days after the initial attack) there was a strong concentration of neutralizing antibodies in the patient's serum against the newly isolated, J. P., A. M. and W. E. (Rivers) strains of choriomeningitis virus. At this time the complement-fixing antibody titer was 1/40.

ANTIBODY STUDIES OF POOLED NORMAL ADULT HUMAN SERUM

Because of the patient's favorable response to pooled normal adult serum,[9] we considered it desirable to test several pools of serum for the presence of lymphocytic choriomeningitis antibodies. Unfortunately, the pooled serum administered to the patient was not available for study. For this reason several other pools of serum selected at random were tested. The results are given in table 3. Of 12 serum pools tested, 3 proved to contain neutralizing

TABLE 3.—*Lymphocytic Choriomeningitis Neutralizing and Complement-Fixing Antibodies in Pooled Normal Adult Human Serum*

Pool No.	Neutralizing Antibodies	Complement-Fixing Antibodies
204	0	0
209	0	0
215	+	Anticomplementary
220	0	0
522	0	0
523	0	0
524	0	0
525	+	0
526	0	0
527	+	0
528	0	0
529	0	0

antibodies, inactivating at least 100 minimal lethal doses of the J. P. strain of choriomeningitis virus. One pool was anticomplementary; the remaining eleven pools contained no complement-fixing antibodies.

COMMENT

There can be no question, from the isolation of the virus in both episodes of the illness and from the subsequent development of virus-neutralizing substances, that this patient suffered an attack and recurrence of lymphocytic choriomeningitis. Armstrong [10] has stated that this ailment in man presents a remarkably variable clinical picture—a meningeal, an encephalomyelitic and a grippal or non-nervous-system type. Despite this consideration, it is extremely difficult to say that all the manifestations in this instance were due to the disease process. The clinical picture at times was so strongly suggestive of hysteria that only few of us entertained the thought that the clinical picture was not a pure hysteria. Naturally, after the virus and immunologic studies we were convinced that the patient had suffered an attack of a real infection. The question may still be raised, however, whether all the symptoms and findings were caused entirely by the infectious process. It is possible that some of the symptoms were due to a hysterical component.

In addition to the unusual clinical manifestations, there were other unique aspects in this case. The patient's temperature was practically normal throughout the illness. Examinations of the spinal fluid disclosed no particular change.

7. Obtained through Dr. Charles Armstrong, of the National Institute of Health.

8. Howitt, B. F.: Viruses of Equine and of St. Louis Encephalitis in Relationship to Human Infections in California, 1937-1938, Am. J. Pub. Health **29**:1083-1097 (Oct.) 1939.

9. Each pool of normal adult human serum consists of approximately 4 liters of serum obtained from 18 to 20 healthy adult urban donors.

10. Armstrong, C.: Some Recent Research in the Field of Neurotropic Viruses with Especial Reference to Lymphocytic Choriomeningitis and Herpes Simplex, Mil. Surgeon **91**: 129-146 (Aug.) 1942.

Of particular interest was the absence of pleocytosis in the spinal fluid. In a previous publication [1b] we have pointed out that the spinal fluid may be normal in the acute stage of lymphocytic choriomeningitis and that only virus and immunologic studies can confirm or rule out the presence of this disease.

The demonstration of neutralizing antibodies for the virus of St. Louis encephalitis was an incidental finding of considerable interest in view of the history that the patient had lived in El Cajon, San Diego County, Calif., and had suffered from a rather obscure illness five years previously. In view of the demonstration of antibodies and the fact that this disease is endemic in California,[11] it is not unlikely that this illness had been a mild attack of St. Louis encephalitis.

Pooled normal adult human serum was administered on an empiric basis, since we felt that the illness might be due to an infection and we hoped that the serum might contain neutralizing antibodies which would be of benefit. The rather spectacular response to the first administration of serum seemed to strengthen the theory that the condition was hysteria. Serum therapy was therefore withheld during the recrudescence and was finally administered only as a last resort measure and without much hope of any effect. We were greatly surprised to witness a response to the second injection of serum comparable to that seen with the initial attack.

In an attempt to explain the improvement coincidental with administration of serum studies were carried out on 12 random pools of normal adult human serum. Unfortunately, we did not save serum from the pools used in treating the patient. The results of titration of these random pools are summarized in table 3 and reveal that 3, or 25 per cent, contained neutralizing antibodies against the choriomeningitis virus. This result is not unexpected, in view of Armstrong's finding that approximately 11 per cent of 2,000 serums from the general population contained such antibodies.[12]

We shall not attempt to draw any conclusions from the use of serum in this single case. Nevertheless, it is a fact that with both episodes of this disease the patient, when appearing in a critical condition, improved markedly promptly after the administration of large amounts of pooled normal adult serum which may have contained neutralizing antibodies for the virus of choriomeningitis. Obviously a great deal of work and study must be carried out before any definite conclusions can be reached.

SUMMARY

In a case of recurrent lymphocytic choriomeningitis the virus was isolated from spinal fluid obtained during the initial attack and again during the recrudescence. The patient subsequently had a strong concentration of both neutralizing and complement-fixing antibodies for the choriomeningitis virus in her blood serum. The case showed several unusual clinical features, especially the clinical picture of an encephalomyelitis associated with absence of pleocytosis or other abnormal findings in the spinal fluid and an essentially afebrile course. Administration of pooled normal adult human serum in large amounts appeared effective in the control of both the first attack and the recrudescence of the disease. The presence of neutralizing antibodies against the virus of lymphocytic choriomeningitis was demonstrated in 3 of 12 random pools of normal adult human serum, while no complement-fixing antibodies were detected.

11. Howitt, B. F.: Human Equine Encephalomyelitis and St. Louis Encephalitis in California, 1939-1941, Am. J. Pub. Health **32**:503-515 (May) 1942.

12. Armstrong, C.: Studies on Choriomeningitis and Poliomyelitis, in Harvey Lectures, series 36, 1940-1941, Lancaster, Pa., Science Press Printing Company, 1941, pp. 39-65.

EFFECT OF ROENTGEN THERAPY ON THE HEART

A CLINICAL STUDY

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The modern treatment of cancer is a group project, requiring the close cooperation of the surgeon, the radiologist and the internist. Among the more important problems with which the internist must deal are the effects of radiant energy on vital structures, such as the gastrointestinal system, the kidneys, the lungs and the heart, in patients who are receiving or have received radiation therapy. The purpose of this paper is to report these effects on the cardiovascular system as they have been observed clinically.

This paper is the fourth in a series from the medical service of Memorial Hospital on the effect of radiation therapy on the heart and the lungs. The first two [1] dealt with the immediate and the late effects of high voltage roentgen rays on the hearts of adult rats. Work now in progress will supplement these reports and is concerned with the pathologic physiology of chronic radiation pleuropulmonitis. A preliminary report on this phase of the subject has already been given.[2]

LITERATURE

A review of the literature shows many reports concerning the effect of roentgen radiation on the hearts of laboratory animals. Warren and Whipple and others [3] failed to find evidence of muscle change macroscopically or microscopically when the heart was subjected to varying doses of roentgen rays. On the other hand, Davis [4] and Hartman and associates [5] provoked alteration of the myocardium by irradiation of the heart. Domagk [6] recorded instances of myocardial fibrosis in

From the Medical Department, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York.

1. Leach, J. E., and Sugiura, K.: (*a*) The Effect of High Voltage Roentgen Rays on the Hearts of Adult Rats, Am. J. Roentgenol. **45**:414-425 (March) 1941; (*b*) The Late Effect of High Voltage X-Rays on the Heart of Adult Rats, ibid., to be published.

2. Leach, J. E.; Farrow, J. H.; Wawro, N. W., and Foote, F. W., Jr.: Fibrosis of the Lung Following X-Radiation for Breast Cancer, Am. J. Roentgenol., to be published.

3. Warren, S. L., and Whipple, G. H.: Roentgen Ray Intoxication: Unit Dose Over Thorax Negative—Over Abdomen Lethal, Epithelium of Small Intestine Sensitive to X-Rays, J. Exper. Med. **35**:187-203 (Feb.) 1922. Gordon, B.; Strong, G. F., and Emery, E. S., Jr.: Effect of Direct Radiation Over Precordium on Heart Size—Heart Mechanism and Myocardium of Rabbits, Am. J. Roentgenol. **11**:328-330 (April) 1924. Warthin, A. S., and Pohle, E. A.: Effect of Roentgen Rays on the Heart; Microscopic Changes in Heart Muscle of Rats and Rabbits Following Single Exposure, J. A. M. A. **89**:1825-1829 (Nov. 26) 1927; Effect of Roentgen Rays on the Heart: Microscopic Changes in Heart Muscles of Rats and of Rabbits Following a Series of Exposure, Arch. Int. Med. **43**:15-34 (Jan.) 1929.

4. Davis, K. S.: Intrathoracic Changes Following X-Ray Treatment: Clinical and Experimental Study, Radiology **3**:301-322 (Oct.) 1924.

5. Hartman, F. W.; Bolliger, A.; Doub, H. F., and Smith, F. J.: Heart Lesions Produced by Deep X-Rays: Experimental and Clinical Study, Bull. Johns Hopkins Hosp. **41**:36-61 (July) 1927.

6. Domagk, G.: Gewebsveränderung nach Röntgenbestrahlungen, Ergebn. d. inn. Med. u. Kinderh. **33**:1-62, 1928.

animals that survived irradiation of the entire body. Leach and Sugiura [1a] found that at least 10,000 r (measured in air) delivered through a precordial port was required to cause capillary hemorrhage and round cell infiltration in the heart muscle. The endocardium and the pericardium resisted single doses up to and including 20,000 r. In another group of animals, killed seven months or more after treatment, myocardial fibrosis was not caused by doses up to and including 7,500 r.[1b]

Clinical observations of the effects of roentgen radiation on the heart are scant. Thibaudeau and Mattick [7] reported postmortem observations on patients who died from cancer and who had received radiation to organs adjacent to the heart. They concluded that cardiac damage might result from roentgen therapy. Gendreau [8] noted the frequent occurrence of cardiac arrythmia of all types in patients while they were undergoing roentgen irradiation of different regions of the body, including the thorax. Desjardins [9] carefully reviewed all of the literature up until 1932 and came to the conclusion that roentgen rays as used clinically at that time (1932) would not cause cardiac damage.

SELECTION OF PATIENTS

This study presented some difficulties. In the choice of patients those required were the ones whose neoplastic disease was not so far advanced that they were likely to die from its effect before adequate follow-up examinations could be made. The ideal patient was one who had a localized cancer, who was in good general condition and who was to receive roentgen therapy alone. In many patients of this type, however, surgical procedures had to be added to the roentgen therapy, and in others distant metastasis developed, with resultant cachexia. Some of the patients were lost track of or died elsewhere, so that adequate postmortem examination was impossible.

Eighty-five patients were selected. They included patients of all ages (except children) and of varied occupations. The great majority fell into the late middle and senile age groups for the obvious reason that cancer is more prevalent in persons of such age groups. There were patients with normal hearts and patients with various types of heart disease, particularly the arteriosclerotic type.

METHOD OF STUDY

Each patient first received a general survey, which included a complete history and physical examination. Each was then examined with special reference to the neoplastic disease for which he originally sought treatment. The second examination varied from a local examination and biopsy for histologic diagnosis to extensive roentgenographic and endoscopic studies. With some patients an aspiration biopsy was done to establish the diagnosis of tumor. None of these procedures caused any change in the local neoplastic process or had any sustained effect on the general well-being of the patient. A third examination consisted of (1) a history with particular reference to the cardiovascular system, (2) a physical examination, (3) a teleroentgen or fluoroscopic examination of the chest and heart and (4) an electrocardiographic examination.

At intervals which varied somewhat with the type of treatment they were to receive, the patients were reexamined and further roentgenograms of the chest and electrocardiograms were made. The time of the second examination was made to coincide as closely as possible with the height of the reaction which resulted from the first course of roentgen therapy. Further examinations were made at intervals up to three months as indicated by the patient's treatment, symptoms and general health. If symptoms or signs of cardiac failure occurred in a patient before, during or after therapy, he was seen at much shorter intervals. If, on the other hand, a patient was obviously doing well, he was seen at the end of three months. The follow-up period for some of the patients was only a few months, since they died early in the course of

7. Thibaudeau, A. A., and Mattick, W. L.: Histological Findings in Hearts Which Have Been Exposed to Radiation in Course of Treatment of Adjacent Organs, J. Cancer Research **13**:251-259 (Oct.) 1929.

8. Gendreau, J. E.: Far Reaching Effects of Gamma Rays and Short X-Rays upon Human Heart, Ann. Surg. **93**:476-480 (Jan.) 1931.

9. Desjardins, A. U.: Action of Roentgen Rays and Radium on Heart and Lungs: Experimental Data and Clinical Radiotherapy, Am. J. Roentgenol. **27**:149 (Jan.); 303 (Feb.); 477 (March) 1932; **28**:127-143 (July); 271-292 (Aug.); 421-436 (Sept.); 567-578 (Oct.); 699-720 (Nov.); 843-858 (Dec.) 1932.

their care or were lost to other institutions for a variety of reasons. Other patients have been followed for over three years.

The electrocardiograms were taken both with an amplifying and with a galvanometer type of machine. All were taken with the subject in the supine position, and the standard limb leads were used. Precordial leads were used with some patients but not with patients in group III (see next section) because of the frequent change in the position of the heart in the thorax following chronic radiation pleuropulmonitis.

GROUPING OF PATIENTS

For purposes of comparison, the patients have been placed in three groups, depending on the location of the original tumor.

Group 1 consists of patients with cancer of the head, neck, cervix uteri or rectum. While these are dissimilar diseases, for this study they have certain features in common. The treatment was largely roentgen irradiation of the tumor and radon seed implantation, and there was a minimum of surgical intervention. Most important, the upper portion of the abdomen and the chest were not irradiated.

Group 2 is a miscellaneous collection of patients who had malignant lymphoma or teratoma. These patients are grouped together because the intrathoracic structures, as well as other parts of the body, received radiation.

Group 3 includes patients with cancer of the breast, lung, esophagus or the cardiac end of the stomach, as well as 1 patient with tuberculosis of the mediastinal lymph nodes. These are placed together because the thorax was the chief region treated and the rest of the body did not receive radiation.

COMPARISON OF RADIATION THERAPY AND ADVERSE EFFECTS IN THE THREE GROUPS

Group 1.—This group is made up of patients with cancer in the following locations:

	Patients
Buccal mucous membrane	1
Floor of the mouth	1
Tongue	2
Tonsil	1
Rhinopharynx	1
Extrinsic larynx	3
Cervix uteri	6
Rectum	5
Sigmoid portion of the colon	1

The group includes 14 men and 7 women, ranging in age from 40 to 82 years. The majority were from 50 to 70 years of age. Eleven patients had no evidence of heart disease. Ten had mild to moderate forms of arteriosclerotic heart disease with variable degrees of hypertension and myocardial fibrosis, with and without mitral incompetency and aortic sclerosis. All had regular sinus rhythm, and only 2 had less than class I functional capacity. These patients had class II functional capacity.

In the patients with cancer of the head and neck the roentgen therapy consisted of a course of radiation therapy through one or more portals. At the height of the ensuing reaction, three to six weeks after starting therapy, gold radon seeds were frequently implanted to supplement the roentgen ray effect. In these patients there usually developed severe mucositis in the treated region with variable degrees of dysphagia or trismus or both. These symptoms were so severe in some patients

TABLE 1.—*Data on Patients in Group 1*

Diagnosis	Name and Treatment *	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Weight Change from Normal †	Dysphagia ‡	Cardiac Symptoms	Comment
1. Cancer of buccal mucous membrane	T. T. 5/16-6/14, 5,600 r left cheek 6/14, 9.30 mc. in lesion 6/28, 4.05 mc. in lesion **9/ 2, 4,800 r to node left side of neck** 9/20, 15.20 mc. in node left side of neck 12/13, 6.09 mc. in node left side of neck	43	M	Essential hypertension	5/16/38, 158/100 6/10/38, 164/100 9/ 6/38, 160/100 12/13/38, 164/102 3/13/39, 172/100	0 0 0 0 0	0 0 0 0 0	None	
2. Cancer of floor of mouth	T. B. 4/18-5/17, 7,800 r to lesion through oral cone 5/17, 10.14 mc. in lesion **5/24, 10.55 mc. in node in neck**	54	M	Normal heart	4/12/38, 130/ 92 5/24/38, 114/ 90 8/11/38, 110/ 85 12/15/40, 114/ 80	0 — 0 0	0 0	None	
3. Cancer of tongue	J. H. 5/26-6/9, 3,000 r by 2 portals to lesion 3,000 r to node in neck 8/9-8/23, 3,300 r by 2 portals to lesion	75	M	1. Hypertension, arteriosclerosis 2. Enlargement of heart, mitral incompetency, aortic sclerosis 3. Regular sinus rhythm 4. Functional capacity I	5/23/38, 170/ 90 7/ 2/38, 146/ 92 10/27/38, 170/100 1/ 6/39, 158/ 96 4/20/39, 170/100	0 — — — 0 0	0 0 0	None	
4. Cancer of tongue	A. S. 5/3, 5,000 r to lesion 5/27, 9.16 mc. in lesion	61	M	1. Hypertension, arteriosclerosis, syphilis 2. Myocardial fibrosis 3. Regular sinus rhythm 4. Functional capacity I	4/29/38, 180/100 5/26/38, 168/100 8/25/38, 152/ 90 11/21/38, 148/ 96 3/ 6/39, 162/ 84 7/18/39 1/ 4/40, 180/100	0 — — + + 0 Normal	.. 0 0 0 0	None	
5. Cancer of rhinopharynx	D. D. P. 4/18-5/6, 4,200 r by 2 portals through cheeks 4,200 r left upper part of neck 5,600 r right upper part of neck	44	M	1. Essential hypertension 2. Enlarged heart 3. Regular sinus rhythm 4. Functional capacity I	4/18/39, 150/120 5/ 6/38, 140/100	0 —	0	None	
6. Cancer of tonsil	G. K. 5/26-6/27, 4,000 r to lesion through oral cone 4,500 r left side of neck 7/22, 33.00 mc. right carotid node 7/22, 6.23 mc. anterior tonsillar pillar 7/28, 22.01 mc. left carotid node	66	M	1. Arteriosclerosis, hypertension 2. Normal heart	4/22/38, 162/ 82 7/12/38, 120/ 92 10/ 7/38, 140/ 90 11/15/38, 128/ 90	0 — — — — — +	0 0	None	
7. Extrinsic cancer of larynx	T. H. 5/31-7/1, 4,200 r each side of larynx	65	M	1. Hypertension, arteriosclerosis 2. Myocardial fibrosis 3. Regular sinus rhythm 4. Functional capacity I	5/31/38, 180/100 7/ 1/38, 120/ 82 10/26/38, 200/110 1/30/39, 180/100 4/27/39, 200/100 1/30/40 10/10/40, 160/100	0 — — — + — ++ + 0	0 +++ ++ 0 0 0	Exertion dyspnea unchanged after radiation reaction subsided	Progressive lowering of T waves up to January 1940; in October 1940 T waves had normal voltage; marked dyspnea and cough at height of radiation reaction
8. Extrinsic cancer of larynx	J. M. **4/19-5/17, 5,200 r each side of larynx** 3,700 r posteervical 7/21-8/15, 4,800 r left side of neck	48	M	Normal heart	4/ 1/38, 112/ 70 5/12/38, 110/ 72 9/ 2/38, 114/ 72	0 — — — —	+++ ++ ++	None	Marked dyspnea and cough at height of radiation reaction
9. Extrinsic cancer of larynx	J. L. 3,500 r each side of larynx 30 mc. right carotid bulb node	64	M	1. Arteriosclerosis 2. Myocardial fibrosis, coronary sclerosis 3. Regular sinus rhythm with anginal symptoms 4. Functional capacity I	4/ 1/38, 160/ 90 5/ 6/38, 140/ 86	0 0	0 ++	Died; probably coronary occlusion	Marked dyspnea and cough at height of radiation reaction

	Mrs. H.	65	F	1. Arteriosclerosis 2. Normal heart	5/16/38 4/21/38, 130/ 82	— — —	..	None	

10. Cancer of sigmoid	Mrs. H. ..... Radium pack	65	F	1. Arteriosclerosis 2. Normal heart	5/16/38 4/21/38, 130/ 82	— — —	..	None	.....
11. Cancer of cervix uteri, League of Nations class III	F. D. ..... 4/12, 750 r by 6 pelvic portals 5/16, 75.7 mc. hr. by vaginal applicator 5/17, 76 mc. hr. cervical tandem 10/25, 17.4 mc. right parametria	47	F	1. Hypertension 2. Normal heart	4/ 4/38, 160/100 4/21/38, 130/ 82 10/ 3/38, 170/110 4/ 3/39, 130/ 90	— — — 0 — — —	..	None	Progressive lowering of T waves as cachexia supervened
12. Cancer of cervix uteri	O. N. ..... 1,000 r by 6 pelvic portals 1,000 mc. hr. by vaginal applicator 2,700 mc. hr. cervical tandem	60	F	Normal heart	4/21/38, 150/ 92 5/ 5/38, 146/ 92	0 —	..	None	.....
13. Cancer of cervix uteri, League of Nations class III	C. L. ..... 200 r by 6 pelvic portals 1,000 mc. hr. cervical bomb 3,000 mc. hr. cervical tandem	73	F	1. Hypertension, arteriosclerosis 2. Enlargement of heart, myocardial fibrosis 3. Regular sinus rhythm 4. Functional capacity I	5/23/38, 170/ 90 7/ 5/38, 148/ 82 10/11/38, 180/100 2/13/39, 168/100 4/17/40, 172/100	0 0 0 0 0	..	Exertion dyspnea unchanged	.....
14. Cancer of cervix uteri	J. S. ..... 7/12-7/19, 750 r by 6 pelvic portals 8/9/38, 3,000 mc. hr. tandem	82	F	1. Hypertension, arteriosclerosis 2. Enlargement of heart, myocardial fibrosis 3. Regular sinus rhythm 4. Functional capacity II	7/11/38, 168/112 8/15/38, 150/100 12/15/38, 160/120 4/10/39, 150/ 90	0 0 — —	None	Nocturnal dyspnea	T waves increased at height of therapy; T waves decreased with digitalization
15. Cancer of cervix uteri	M. M. ..... 8/10-9/3, 1,700 r by 6 pelvic portals 10/3, 1,000 mc. hr. cervical bomb 10/4, 3,000 mc. hr. cervical tandem	40	F	Normal heart	8/ 1/38, 132/ 80 9/24/38, 104/ 78 11/ 3/38, 117/ 80	0 — — —	None	None	.....
16. Cancer of cervix uteri	E. B. ..... 1,700 r by 4 pelvic portals 8/33, 1,000 mc. hr. cervical bomb 3,000 mc. hr. cervical tandem	51	F	Normal heart	6/ 8/38, 138/ 80 138/ 90	0 0	None	None	.....
17. Cancer of rectum	H. B. ..... 900 r by 4 pelvic portals	57	M	1. Buerger's disease 2. Coronary sclerosis 3. Regular sinus rhythm with anginal symptoms 4. Functional capacity II	11/10/38, 160/ 92 12/28/38, 162/ 98	0 0	None	Anginal syndrome unchanged	.....
18. Cancer of rectum	N. S. ..... 900 r by 6 pelvic portals 700 r perineal portal 4 mc. hr. rectal applicator	67	M	1. Arteriosclerosis 2. Normal heart	4/26/38, 160/100 6/ 2/38, 150/ 92 8/16/38, 140/ 82	0 — —	None	None	T waves progressively lowered as cachexia supervened
19. Cancer of rectum	I. S. ..... 450 r by 4 pelvic portals 10 mc. hr. rectal applicator	70	M	Normal heart	5/10/38, 150/ 82 5/31/38, 142/ 80 9/29/38, 140/ 82	0 0 — —	None	None	T waves progressively lowered with cachexia
20. Cancer of rectum	D. B. ..... 900 r to perineum 1,200 r by 2 posterior pelvic portals 2,060 mc. hr. rectal applicator	82	M	1. Arteriosclerosis 2. Myocardial fibrosis 3. Regular sinus rhythm with premature ventricular contraction 4. Functional capacity II	6/ 9/38, 148/ 80 6/30/38, 146/ 60	0 —	None	Exertion dyspnea unchanged	.....
21. Cancer of rectum	M. W. ..... 900 r by 7 pelvic portals 3,200 mc. hr. rectal applicator	54	M	1. Hypertension, arteriosclerosis, obesity 2. Enlargement of heart, myocardial fibrosis 3. Regular sinus rhythm with anginal symptoms 4. Functional capacity I	4/18/38, 130/110 5/10/38, 142/ 82 9/29/38, 145/ 90 12/ 1/38, 152/ 98 12/15/40, 160/110	0 — — + +	None	Progressive exertion dyspnea; increasing anginal pain; in mild failure on two occasions	T wave voltages progressively lowered as patient's cardiac symptoms increase

* In column headed "Name and Treatment" *r* means roentgen units; mc., millicuries of radium; mc. hr., millicurie hours of radium therapy. Such an expression as "3,000 r by 2 portals" means that the stated dose was given through each portal.

† In the column headed "Weight" the sign — means that the loss of weight was mild; — —, loss of weight was moderate; — — —, loss of weight was marked; +, patient was regaining lost weight.

§ In column headed "Dysphagia" or "Toxemia" or "Anemia" the sign + means mild; ++, moderate; +++, marked.

that liquids were the only form of nourishment for a time. Loss of weight was marked in some patients. Dyspnea, persistent cough, aspiration and obstructive tracheobronchitis due to laryngeal and pharyngeal edema, infection of the tumor and faulty deglutition frequently developed in addition to dysphagia in those patients with radiation directed to the larynx and the hypopharynx.

Patients with cancer of the cervix uteri usually had a pelvic cycle up to 1,800 r through four pelvic portals, followed in six weeks by a cervical tandem of 3,000 to 3,600 milligram hours of radium. The latter treatment had to be delayed in some instances because of cervical stenosis and secondary pyometra. Moderate radiation nausea and vomiting which interfered with nutrition and maintenance of weight developed in some patients. Local infection of the tumor, uterine infection and secondary anemia were not uncommon. The radiation reaction and bleeding tended to decrease the patients' strength.

The patients with rectal cancer received an average dose of 950 r by four pelvic portals plus local radium therapy by means of a special applicator. Many after treatment experienced severe gastrointestinal symptoms with anorexia, abdominal cramps, diarrhea and marked rectal tenesmus. These factors often interfered with adequate rest and nutrition.

Loss of weight was most marked in the group with cancer of the head and neck and was present to a lesser extent in the group with pelvic cancer. This was due to the marked dysphagia usually present at the height of the radiation reaction in the patients with cancer of the head and neck and to the longer period of active treatment which they underwent.

An appreciable drop in blood pressure was noted in only 4 patients with pelvic neoplasms whereas 6 of the 9 patients with cancer of the head and neck had a moderate to marked decrease of blood pressure. In the latter this decrease was roughly proportional to the loss of weight. In the group with pelvic cancers some of the patients losing weight had decreased blood pressure and some did not.

The fall in the blood pressure of patients receiving roentgen therapy (fig. 1) has been attributed by some investigators to absorption of split protein (histamine-like) substances secondary to destruction of tissue. This may be true, but deficient intake of food with the attendant loss of weight would seem to play a more important role in these patients. This change in blood pressure was not necessarily dependent on the presence of antecedent heart disease or previous hypertension. As the reaction subsided, many of the patients tended to regain their former level of blood pressure.

The serial electrocardiograms were interesting but somewhat confusing. The voltage of P waves and the QRS complexes varied to a moderate degree. There was no variation of the auriculoventricular conduction times. The voltage of the T waves also varied in some. These changes were not proportional to previous cardiac disease, alteration of the blood pressure, loss of weight, toxemia, severity of the radiation reaction at its height or to type of neoplastic disease present. Probably the changes noted depended on the interplay of all these factors, some more important than others, but too complicated to permit accurate analysis. One point was especially striking. This was the gradual lowering of the voltage of all the waves, especially of the T waves, in patients who were suffering from cachexia due to widespread cancer. Simon and Baum[10] noted similar T wave changes

10. Simon, S., and Baum, F.: Electrocardiographic Studies in Pulmonary Tuberculosis: Preliminary Report on Two Hundred and Fifty Cases, Am. Rev. Tuberc. **17**:159-181 (Feb.) 1928.

in patients who were suffering from terminal pulmonary tuberculosis. Their explanation that this represented a result of progressive depression of the myocardium due to toxemia probably applies to these patients with terminal cancer.

Outstanding cardiac complications following therapy were observed in 2 of the 21 patients. One was a man with cancer of the larynx who had symptoms of coronary sclerosis with angina of effort and who had had cardiac failure two years before, for which he had been treated by his family physician. He received fairly heavy roentgen radiation to his larynx. At the height of the reaction he complained of incessant cough with expectoration and increasing dyspnea with effort, due to the marked edema of the larynx and obstructive tracheobronchitis. He did not complain of any increased cardiac pain at the time. Three months later he died suddenly at home as a result of a heart attack, presumably a coronary occlusion.

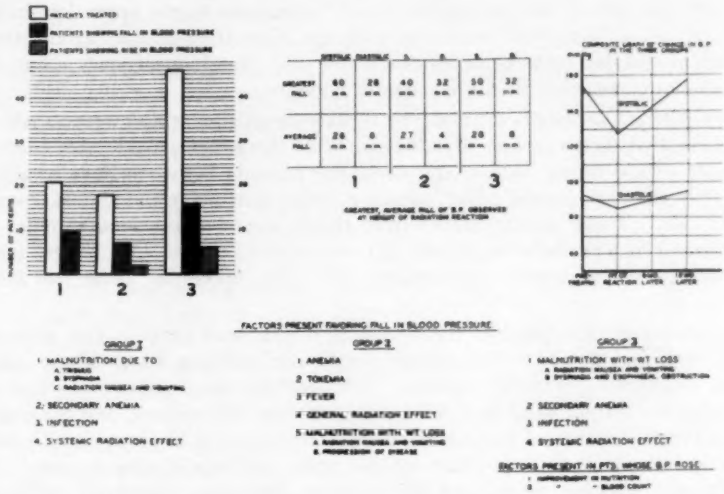


Fig. 1.—The effect of high voltage roentgen therapy on the blood pressure of 85 patients treated for cancer. The presence of hypertension or heart disease or both did not influence these results. Group 1 includes 21 patients with cancer of the head, neck, cervix uteri or rectum; roentgen radiation was directed to these areas; but the thorax was not irradiated. Group 2 includes 18 patients with lymphoma or teratoma; roentgen therapy was directed to various parts of the body including the thorax. Group 3 includes 42 patients with cancer of the breast, lung, esophagus or cardiac end of the stomach, 3 with other types of neoplastic diseases and 1 with tuberculosis of the mediastinal lymph nodes; only the thorax was irradiated.

The second patient, a woman of 82 years with a cervical cancer, had hypertension with an enlarged heart and mitral incompetency for some years prior to treatment. An electrocardiogram made before treatment showed auricular premature systoles. She had relatively little difficulty during the time she received roentgen and radium tandem therapy. Five months later she complained of palpitation and dyspnea and on examination was found to have an increased degree of hypertension and auricular fibrillation with a rapid ventricular rate. At the same visit she was found to have a large pyometra.

After careful consideration one cannot attribute the coronary occlusion in the one patient and the auricular fibrillation in the other patient to roentgen therapy per se. While it is true that in the man the laryngeal edema, tracheobronchitis and incessant cough may have helped to precipitate the coronary occlusion, a nonspecific infection of the respiratory tract could have conceivably produced the same result. In the woman the pyometra, toxemia and anemia possibly played a part in precipitating the arrhythmia, but these conditions are not necessarily secondary to roentgen therapy and can arise in the course of various pelvic diseases.

It would be well to mention at this point 3 other patients not included in group 1 who have been observed over the past two years. They had carcinoma of the floor of the mouth, the tongue and the hypopharynx, respectively. The first had a normal cardiovascular system; the second had generalized arteriosclerosis with myocardial fibrosis, and the third a mild degree of generalized arteriosclerosis without demonstrable heart disease. Oddly enough, all the primary lesions were on the left side, and all the patients had bulky metastases to the upper left cervical nodes, i. e., those intimately associated with the bifurcation of the carotid artery. Two had, in addition to local metastases, a necrotic, sloughing primary lesion with an inflammatory reaction in the metastatic nodes.

The symptoms and signs exhibited by them were all similar and were as follows: At the height of their reaction to radiation, when there was considerable edema of the tissues of the lateral side of the neck, the patients began to have attacks of syncope preceded by marked pallor, sweating, feeble slow pulse and almost inaudible heart sounds. These attacks lasted from thirty seconds to several minutes and were followed by a period of weakness and some apprehension. One patient fainted five times in one hour after examination in the follow-up clinic. None had fainted before.

On observing these patients the following points were noted. The pulse first became weak and slowed rather abruptly until the rate was 40 to 50 per minute with an occasional premature systole. The systolic blood pressure, which had been within normal limits at first, fell to 60 to 80 mm. of mercury, and the patients became extremely pale and fainted. The pulse continued to be slow, and 2 patients made slightly spasmodic movements of the arms and legs during syncope. The attacks lasted variable times, and the patients frequently recovered before any stimulants were given. Of 2 patients tested by pressing over the involved cervical nodes, the first had an abrupt slowing of the pulse and the second complained of vertigo.

One must conclude from the type of attack and the presence of infected metastatically involved cervical nodes that these were instances of carotid sinus syncope.

These patients responded quickly to large doses of atropine. The atropine effect was maintained for a few days, with tincture of belladonna administered by mouth until the infection subsided. The attacks ceased and did not recur. One patient continued to have the attacks for a week despite the added use of ephedrine sulfate ¾ grain (0.045 Gm.) given four times daily by mouth.

No attacks of this type have been observed in patients who had radical cervical dissections, in many of whom the vagus nerve was sacrificed. None has been observed in those patients in whom the vagus nerve was possibly destroyed by implantation of radon seeds in metastatically involved nodes in the neck. When the vagus nerve is severed or destroyed, the contralateral nerve is sufficient to carry the normal regulatory impulse to and from the heart and aorta and the contralateral sinus.

Group 2.—The second group is made up of patients with the following types of cancer:

	Patients
Brill-Symmer disease (giant follicular lymphoma)	1
Hodgkin's disease	10
Lymphosarcoma	2
Teratoma testis with widespread metastases	2
Lymphatic leukemia	3

These patients are grouped together because of the anatomic similarity of all these diseases except teratoma and because their treatment was directed to widely scattered regions in the body, including the thorax. The usual practice is to treat patients with these diseases less vigorously than patients with epidermoid carcinoma or adenocarcinoma. However, the 2 patients with teratoma were given heavy doses of radiation over an extended period. The ages ranged from 22 to 71 years, and there were 12 men and 6 women. Five patients had heart disease; in 2 it was rheumatic in origin, and in 3 it was secondary to hypertension and arteriosclerosis. These patients all had class I functional capacity with the exception of patient 17 (table 2), who had class II functional capacity.

Treatment of patients in this group differed widely. Roentgen radiation was given in doses totaling from 400 to 2,000 r to single portals and these were repeated or not, depending on the course of the individual patient's disease. The 2 patients with lymphosarcoma were treated more vigorously than the 10 with Hodgkin's disease. The 3 with lymphatic leukemia each received 75 r in the Heublein unit (irradiation of the whole body).

A drop in blood pressure was observed in 7 patients; 9 others had essentially no change in blood pressure and in 2 patients the blood pressure was higher at the end of treatment than it had been on admission to the clinic (fig. 1). While there was no apparent direct relation between the decrease of the blood pressure in the 7 patients and anemia, toxemia, fever and general radiation effect, all or some of these factors were present and undoubtedly played major roles in lowering the blood pressure after roentgen therapy. The blood pressure continued to fall in some of the patients as the disease became generalized.

Loss of weight was not a prominent factor in the patients of this group. In fact, they either maintained their admission weight or gained during the time they received the first cycle of roentgen therapy. This was particularly true in those with Hodgkin's disease who were toxic and anemic before treatment. Some had fever before treatment was started. Later on, as the disease progressed, loss of weight was marked in some.

The serial electrocardiograms in this group were interesting. The P wave voltage and the PR and QRS intervals were unchanged. There were slight changes in the QRS voltage in all patients except 1 in whom the changes were marked. Changes in T wave voltage were common and varied widely. In some patients all the T waves were increased; in others only T_1, T_2 or T_3 was increased. However, the increases did not follow any pattern. One patient with advanced Hodgkin's disease who was very cachectic showed all the T waves lowered as in the patients with generalized carcinomatosis in group 1. In group 2 the generalized nature of the neoplastic disease, the fever, the anemia, the toxemia and the depressing effect of the radiation itself possibly contributed all or in part to the electrocardiographic changes. One could not link these changes with heart disease secondary to the roentgen therapy.

TABLE 2.—*Data on Patients in Group 2**

Diagnosis	Name and Treatment	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Weight Change	Toxemia	Anemia	Comment
1. Hodgkin's disease	L. W. 5/27, 2,000 r by 2, anterior and posterior mediastinum 10/4, 700 r by 4 directed at cervix	56	F	Normal heart	5/26/38, 122/ 70 6/22/38, 108/ 80 7/21/38 2/17/39, 112/ 80	— — 0 ++	++ 0 0 0	++ 0 0 0	
2. Hodgkin's disease	S. Y. 900 r by 2, anterior and posterior mediastinum	25	F	Normal heart	4/25/38, 120/ 80 5/12/38, 106/ 70 7/14/38, 104/ 88	— + — —	++ 0 +++	0 0 +++	Cachectic; pleural effusion on left 7/14/38
3. Hodgkin's disease	S. M. 4/2/39, 1,200 r by 2, right and left side of neck 1,200 r by 2, anterior and posterior mediastinum 9/26, 800 r right supraclavicular space	34	F	1. Hypertension and obesity; normal heart	3/28/39, 160/112 5/ 4/39, 120/ 80 12/28/39, 120/ 90	0 — —	++ 0 0	0 ++ ++	
4. Hodgkin's disease	D. N. Dec. 1938 to March 1939, 600 r by 2, left side mediastinum, anterior and posterior 900 r by 2, upper mediastinum, anterior and posterior 1,000 r by 2, left upper chest, anterior and posterior 1,000 r supraclavicular space	28	F	Normal heart	10/25/38, 102/ 78 4/20/39, 112/ 80	— — — —	+ +++	+ +++	T waves decreased in voltage as cachexia supervened
5. Hodgkin's disease	M. S. 3,000 r by 2, right side upper neck 4,800 r right side lower neck	71	F	1. Hypertension, arteriosclerosis 2. Enlargement of heart, mitral incompetency 3. Regular sinus rhythm 4. Functional capacity I	4/29/38, 170/106 5/19/38, 210/100	— —	— 0	++ ++	
6. Hodgkin's disease	D. E. 4/6-4/27, 1,800 r by 2, mediastinum, anterior and posterior	54	M	Normal heart	4/7/38, 112/ 80 5/5/38, 114/ 84	0	++ 0	— +	
7. Hodgkin's disease	F. C. 550 r right side upper neck 800 r left side upper neck 550 r right side lower neck 900 r left side lower neck 550 r right axilla 900 r left axilla	53	M	Heart normal	4/25/38, 110/ 82 5/16/38, 114/ 82	— 0	+ 0	0 +	
8. Hodgkin's disease	L. B. July 1938, 1,060 r neck October, 900 r by 2, mediastinum, anterior and posterior December, 50 r Hueblein unit February-April, 1,600 r abdomen	44	M	Normal heart	10/14/38, 142/ 80 11/10/38, 118/ 92 12/23/38, 124/ 80 12/27/38, 96/ 82 1/17/39, 120/ 80 4/28/39, 122/ 88	— 0 — — — — —	+ 0 0 0 + ++	++ ++ ++ ++ ++ +++	

9. Hodgkin's disease	F. S.	50	M	1. Hypertension 2. Cardiac enlargement 3. Regular sinus rhythm 4. Functional capacity I	6/10/38, 180/100 7/29/38, 142/106 12/15/38, 140/ 90 3/ 9/39, 145/ 95	— + + —	++ 0 0 0	++ ++ 0 ++	
10. Lympho-sarcoma	Dr. F. 10/17-11/12/38, element pack 30,000 mg. hr. upper abdomen 11/2-11/12/38 600 r by 2, mediastinum, anterior and posterior 10/17-11/12/38, 600 r by 2, right and left axilla; 900 r left side neck; 600 r left supraclavicular space 6/14/40, 8 abdominal quadrants, 100 r to each	42	M	Normal heart	10/28/38, 120/ 82 11/ 7/38, 110/ 62 11/18/38, 124/ 82 3/13/39, 124/ 80 6/27/39, 144/ 96 11/22/40, 132/ 80	0	0 0 0 0 0 0	0 0 0 0 0 0	
11. Hodgkin's disease	A. N. 1,200 r by 2, mediastinum, anterior and posterior 1,200 r axilla 800 r abdomen 1,200 r left side neck	30	M	Normal heart	4/20/39, 128/ 84 5/16/39, 124/ 78	—	++ 0	0 0	
12. Lympho-sarcoma	C. B. 1,600 r by 2, mediastinum, anterior and posterior 1,500 r right side neck	30	M	Normal heart	3/31/39, 134/ 90 5/ 5/39, 118/ 80	0	+ 0	0 0	
13. Brill-Symmer disease (giant follicular lymphoma)	J. J. 400 r by 6, right and left side neck, right and left axillas and right and left groins	22	M	1. Rheumatic type 2. Cardiac enlargement, mitral insufficiency, mitral stenosis 3. Regular sinus rhythm 4. Functional capacity I	12/27/38, 112/ 95 1/23/39, 110/ 80 3/27/39, 114/ 76	0	0 0 0	0 0	
14. Teratoma testis	J. N. 1,750 r to right side abdomen, anterior 1,750 r to right side abdomen, posterior 3,500 r to epigastrium, anterior 3,500 r to epigastrium, posterior	33	M	Normal heart	6/ 9/38, 110/ 60 8/16/38, 130/ 90	— +	+++ +	++ +	
15. Teratoma testis	R. R. 2,000 r by 2, lower abdomen 2,000 r by 2, epigastrium, anterior and posterior 2,000 r by 2, mediastinum, anterior and posterior	28	M	Normal heart	5/ 2/38, 130/ 80 6/16/38, 102/ 76 8/18/38, 130/ 90	0 0 +	+ + 0	0 0 0	
16. Lymphatic leukemia	J. C. 75 r Hueblein unit	63	M	1. Hypertension, arteriosclerosis 2. Cardiac enlargement, myocardial fibrosis, mitral incompetence, aortic sclerosis 3. Regular sinus rhythm 4. Functional capacity I	10/21/38, 140/ 82 10/24/38, 148/ 90	0 0	++ ++	+ +	
17. Lymphatic leukemia	R. H. 75 r Hueblein unit	30	F	1. Rheumatic fever (inactive), hypertension, arteriosclerosis 2. Cardiac enlargement, mitral insufficiency, myocardial fibrosis 3. Regular sinus rhythm 4. Functional capacity II	7/16/38, 140/ 82 7/17/38, 140/ 82 7/18/38, 160/ 82 10/31/38, 178/ 98	0 0 0 —	+ + + ++	0 0 0 0	
18. Lymphatic leukemia	S. K. 75 r Hueblein unit	65	M	Normal heart	7/15/38, 120/ 64 7/17/38, 120/ 60 7/18/38, 140/ 60	0 0 0	0 0 0	0 0 0	

* See table 1 for key to table.

One patient with marked QRS and T wave changes in the post-treatment electrocardiogram had changes in the position of the heart secondary to a pleural effusion on the left side and infiltration of the lower lobe of the left lung with Hodgkin's disease, which undoubtedly accounted for the alterations in the electrocardiogram.

Group 3.—This group with exception of the patient with tuberculous lymph nodes consists of patients with cancer in the following locations:

	Patients
Left breast	15
Right breast	10
Right lung	5
Left lung	6
Esophagus	4
Cardiac end of the stomach	2
Pleura, left side (mesothelioma)	1
Hilus of the left lung (metastatic teratoma)	1
Mediastinum (Hodgkin's disease)	1
Mediastinal lymph nodes (tuberculosis)	1

These patients are placed in the same group because they received fairly heavy radiation to the thorax, and distant parts of the body were not irradiated. There were 17 men and 29 women, ranging in age from 26 to 73 years. Nineteen of the 46 patients had structural heart disease. In 17 patients the heart disease was secondary to hypertension or arteriosclerosis or both; in 1 it was rheumatic in origin and in 1 syphilitic in origin (table 3).

Most patients with carcinoma of the breast received roentgen radiation to the affected breast and axilla through five portals, each portal being given a total of 1,800 r. In some patients this was followed by radical mastectomy. In those patients to whom only a postoperative cycle was given, the axilla alone was given a dose of 1,800 r to each of three portals. Patients with cancer of the lung received radiation through two or three appropriate-sized portals, cross firing the lesion. The total dose for these patients ranged from 2,000 r to 4,200 r per portal. Patients with cancer of the esophagus were treated through two paravertebral and two parasternal portals. Each portal was given from 1,600 to 3,000 r. The remaining 6 patients (those with teratoma, Hodgkin's disease, tuberculosis, etc.) had types of treatment too varied to permit detailed explanation.

In 15 patients the beam of radiation was directed through the bulk of the heart. In 2 patients the lower half of the heart was irradiated. The doses that these hearts received have been accurately estimated. They ranged from 750 r to 5,200 r. The majority of the doses of high voltage radiation were of the order of 1,500 to 2,500 r.

In an undetermined number of the remaining 29 patients (26 with cancer of the breast, 3 with cancer of the lung) only a portion of the heart was irradiated. This needs some further explanation. The radiotherapeutist in treating cancer of the breast attempts to encompass the lesion and at the same time direct the beam tangentially to the wall of the chest to spare the lung. This was impossible in certain instances because of the location of the lesion or the type of breast with which he had to deal. In these instances the dose that the heart received cannot be estimated.

There were wide variations in blood pressure in the patients of group 3. In 24 it was essentially unchanged during the active phase of radiation therapy; in 16 it fell, and in 6 it was higher at the end of the therapy than before treatment was started (fig. 1). Of the 6 patients whose blood pressure rose, 3 had gastrostomy for marked esophageal obstruction before treatment and their nutrition improved markedly during the time that they received roentgen radiation. This again suggests that the maintenance of nutrition is a factor in affecting the blood pressure during radiation therapy just as it was in the patients who had cancer of the head and neck whose blood pressure fell because of insufficient nourishment.

In the entire group there was no evident correlation between alteration of the blood pressure and heart disease, hypertension, anemia, toxemia, infection or the amount of radiation given.

A comparison of the serial electrocardiograms of these patients taken before, during and after roentgen therapy is most interesting. As in groups 1 and 2, there were no significant or permanent changes in the P wave voltages, and the PR and QRS intervals remained constant except in a single instance (see the section entitled arrythmias, paragraph 4).

The QRS voltage varied widely, frequently and inconsistently. The Q waves were the least affected. The R and S waves were altered as much as 50 per cent from one tracing to its successor. It did not appear to matter whether the right side or the left side of the thorax or the heart itself was irradiated. As a result of these QRS changes, the axis deviation was without its usual import, since the shift was frequently opposite to or greater than the expected one.

On the other hand the changes in T_1 and T_3 were predictable in about 80 per cent of the cases. In those patients who had the area of a cancer of the left breast irradiated either before or after operation, there was a progressive lowering of T_1 even to a negative phase, followed by a gradual rise toward the pretreatment level. Coincident with the decrease of T_1 there was a rise in the voltage in T_3 followed by a gradual decrease toward its former level. T_2 was raised in some tracings and lowered in others and relatively unchanged in still others (figs. 2 and 3).

Conversely, in the patients who had roentgen treatment for carcinoma of the right breast there was a general rise in T_1 followed later by a decrease toward its former level. As T_1 rose, T_3 fell, and then gradually returned to its former level. T_2 rose, fell or remained unchanged (fig. 4). However, these changes were of smaller magnitude than those in the patients who had the left side of the thorax treated.

In those patients in whom the center of the thorax was treated—for instance, patients with carcinoma of the esophagus, carcinoma of the lung close to the hilar area or mediastinal tumors—there were reciprocal changes in T_1 and T_3, but they did not conform to the pattern shown by the patients with cancer of the breast and cancer of the lung away from the hilus (fig. 5).

Three patients have been observed 2 of whom had pericarditis and the third of whom probably has pericarditis following roentgen treatment. In the first, a woman with cancer of the left lung who was treated heavily twelve years ago, radionecrosis of the ribs developed with secondary empyema and a most severe form of pleuropulmonitis. During the last two years of her life progressive right-sided heart failure developed with all its classic signs, and she died as a result of it. At autopsy chronic pericarditis, partly adhesive in type, and the changes typical of chronic cor pulmonale were encountered. The latter state was induced by compression and torsion of the pulmonary artery due to advanced chronic fibrosing mediastinitis.

TABLE 3 A.—*Data on Patients in Group 3: Right Breast and Lung* *

Diagnosis	Name and Treatment	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Comment
1. Cancer of right breast	E. P. ..... August 1938: breast, medial and lateral; supraclavicular space, anterior and posterior; axilla—2,100 r by 5, 200 kv., at 50 cm. S.T.D. Oct. 18, 1938: mastectomy	30	F	Normal heart	8/ 1/38, 114/ 78 8/29/38, 104/ 72 3/14/39, 114/ 80	Cough and dyspnea due to radiation fibrosis of right lung
2. Cancer of right breast	A. W. ..... May 1938: breast, medial and lateral, 1,200 r by 2. June 16, 1938: mastectomy. September 1938: right supraclavicular space, anterior and posterior; axilla—1,200 r by 3. November 1938: chest, anterior and lateral, 2,400 r by 2.	65	F	1. Arteriosclerosis 2. Myocardial fibrosis 3. Regular sinus rhythm 4. Functional capacity I	5/17/38, 140/ 80 9/30/38, 146/ 90 10/28/38, 142, 90 11/21/38, 128/ 60 2/ 7/39, 160/ 84 6/ 5/39, 170/ 98	Cough and dyspnea persistent due to fibrosis of right lung
3. Cancer of right breast	M. S. ..... March 1939: right supraclavicular space, anterior and posterior; axilla direct—1,800 r by 3. July 5, 1939: mastectomy	36	F	Normal heart	3/27/39, 122/ 80 4/29/40, 130/100	.....
4. Cancer of right breast	M. M. ..... April 1939: breast, medial, lateral and inferior; supraclavicular space, anterior and posterior; axilla—2,100 r by 6. Aug. 26, 1939: mastectomy	52	F	1. Hypertension 2. Cardiac enlargement, myocardial fibrosis, mitral incompetence 3. Regular sinus rhythm 4. Functional capacity I	4/ 5/39, 170/ 90 12/14/39, 150/ 90 1/11/40, 154/ 90	Dyspnea due to radiation fibrosis of right lung
5. Cancer of right breast	Y. B. ..... March 1939: breast, medial and lateral; supraclavicular space, anterior and posterior; axilla—2,100 r by 5. August 1939: mastectomy	44	F	Normal heart	3/14/39, 130/ 90 4/20/39, 130/ 82 8/28/39, 124/ 90 10/ 9/39, 138/ 88 1/12/40, 132/ 90 4/14/40, 130/ 90	.....
6. Cancer of right breast	A. M. ..... May 1938: breast, medial and lateral; supraclavicular space, anterior and posterior; axilla—2,100 r by 5.	52	F	Normal heart	5/26/38, 150/ 98 6/20/38, 120/ 90	.....
7. Cancer of right breast	H. K. ..... June 1939: supraclavicular space, anterior and posterior; axilla—1,800 r by 3	64	F	1. Hypertension, arteriosclerosis 2. Cardiac enlargement, mitral incompetence, aortic sclerosis 3. Regular sinus rhythm 4. Functional capacity I (or II)	5/ 2/39, 190/100 5/29/39, 162/ 90 12/28/39, 154/ 90 3/10/40, 160/ 90 10/24/40, 160/ 86	Chronic pleuritis at apex of right lung following radiation therapy

8. Cancer of right breast	R. H. C. March and April 1939: breast, medial and lateral; supraclavicular space, anterior and posterior; axilla—1,800 r by 5	59	F	1. Hypertension, arteriosclerosis 2. Cardiac enlargement, myocardial fibrosis, mitral incompetence, aortic sclerosis 3. Regular sinus rhythm 4. Functional capacity II	3/14/39, 240/120 5/16/39, 210/120 7/16/39, 190/100 11/13/39, 200/110 2/26/40, 210/120	Unchanged; headache and vertigo due to hypertension
9. Cancer of right breast	F. C. June-July 1938: breast, medial, lateral and inferior; supraclavicular space, anterior and posterior; axilla—2,100 r by 6	63	F	1. Hypertension, arteriosclerosis 2. Cardiac enlargement, aortic sclerosis 3. Regular sinus rhythm 4. Functional capacity I (or II)	6/16/38, 160/104 7/14/38, 148/ 88	.....
10. Cancer of right breast	E. V. J. Breast, medial and lateral; axilla; supraclavicular space, anterior and posterior—2,400 r by 5	49	F	1. Hypertension, arteriosclerosis 2. Myocardial fibrosis, aortic sclerosis 3. Regular sinus rhythm with anginal syndrome 4. Functional capacity I	5/ 4/39, 180/110 5/25/39, 160/ 90	.....
11. Cancer of right lung	L. M. June 1938: chest, anterior and posterior, 1,950 r by 2 October 1938: chest, anterior and posterior, 1,350 r by 2 November 1938: chest, anterior and posterior, 3,000 r by 2	58	M	Normal heart	4/21/38, 140/ 88 5/ 3/38, 158/ 90 7/28/38, 164/ 90 10/11/38, 132/ 90 11/ 1/38, 120/ 86 12/14/38, 150/ 90	Cough and dyspnea persistent during period of observation
12. Cancer of right lung	M. B. January 1939: chest, anterior and posterior, 3,800 r by 2 July 1939: chest, anterior and posterior, 2,400 r by 2	52	M	Normal heart	12/30/39, 118/ 76 2/ 2/40, 160/ 90 3/17/40, 142/ 80 4/8/40, 148/ 80 8/22/40, 130/ 80	.....
13. Cancer of right lung	A. P. April 1938: right supraclavicular space, 1,500 r; right axilla, 1,000 r	68	M	Arteriosclerosis, normal heart	4/26/38, 120/ 82 5/15/38, 112/ 78	.....
14. Cancer of right lung	H. G. January 1939: chest, anterior and posterior, 4,000 r by 2 June 1939: mediastinum, anterior and posterior, 1,000 r by 2	60	M	Normal heart	1/20/39, 140/ 80 3/17/39, 140/ 90 5/ 2/39, 138/ 80	.....

* See table 1 for key to table.

TABLE 3 B.—*Data on Patients in Group 3: Left Breast and Lung* *

Diagnosis	Name and Treatment	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Comment
1. Cancer of left breast	E. M. ..... July 1938: supraclavicular space, anterior and posterior 10 by 13 cm.; axilla—1,800 r by 3; May 27, 1938: mastectomy	36	F	Normal heart	5/13/38, 110/ 72 7/17/38, 124/ 82	.....
2. Cancer of left breast	R. W. ..... July 6, 1938: radical mastectomy. Aug. 15, 1931: supraclavicular space, anterior and posterior; axilla direct—1,800 r by 3	37	F	1. Rheumatic fever (inactive) 2. Cardiac enlargement, mitral insufficiency, mitral stenosis 3. Regular sinus rhythm 4. Functional capacity I	6/10/38, 106/ 80 7/21/38, 102/ 80 9/23/38, 112/ 78 1/ 3/39, 100/ 64 6/19/39, 112/ 90	Signs of pulmonary fibrosis; roentgen evidence of fibrosis of left lung
3. Cancer of left breast	M. J. ..... April-May 1938: breast, medial and lateral, 1,800 r each; breast, 4 portals, 600 r each; supraclavicular space, anterior and posterior, 1,800 r each; axilla 1,800 r	51	F	1. Syphilis 2. Cardiac enlargement, aortic insufficiency 3. Regular sinus rhythm 4. Functional capacity I	4/11/38, 160/ 40 5/12/38, 200/ 50 8/18/38, 182/ 60 11/21/38, 200/ 60 2/14/39, 170/ 58	Signs of pulmonary fibrosis; roentgen evidence of fibrosis of left lung
4. Cancer of left breast	A. A. ..... October 1938: breast, direct and lateral, 1,800 r each; supraclavicular space, anterior and posterior, 1,800 r each; axilla 1,800 r	67	F	1. Hypertension, arteriosclerosis 2. Cardiac enlargement, mitral incompetence 3. Regular sinus rhythm 4. Functional capacity I	10/11/38, 210/110 10/21/38, 210/110 11/ 3/38, 200/106 2/ 7/39, 180/ 90	Symptoms of acute radiation pneumonitis
5. Cancer of left breast	L. F ..... March 1939: breast, lateral and medial, 2,000 r each; breast, inferior, 2,400 r; supraclavicular space, anterior and posterior, 2,000 r each; axilla, 2,000 r	63	F	1. Hypertension 2. Cardiac enlargement 3. Regular sinus rhythm 4. Functional capacity I	3/ 9/39, 200/100 4/ 6/39, 210/100	Symptoms of acute radiation pneumonitis
6. Cancer of left breast	R. C. ..... June 1938: breast, lateral, medial and inferior, 2,250 r each; axilla, anterior, posterior and direct; 1,800 r each; Aug. 12, 1938 mastectomy	64	F	1. Arteriosclerosis 2. Myocardial fibrosis 3. Regular sinus rhythm 4. Functional capacity I	5/26/38, 150/ 80 7/11/38, 108/ 68 11/28/38, 118/ 92 1/27/39, 126/ 82 3/27/39, 134/ 80 5/ 8/39, 120/ 82	Signs of pulmonary fibrosis in left lung
7. Cancer of left breast	C. C. ..... June and July 1938: breast, medial and lateral, 2,100 r each; axilla, anterior, posterior and direct	47	F	Normal heart	6/24/38, 140/ 85 8/ 8/38, 138/ 90 9/26/38, 134/ 88 12/12/38, 130/ 80 3/14/39, 152/ 90 6/ 7/39	Signs of chronic radiation fibrosis in left lung

8. Cancer of left breast	L. L. ..... May 1939: breast, lateral, medial and inferior, 2,400 r each; supraclavicular space, anterior and posterior; axilla—2,100 r each. July 15, 1939: mastectomy	43	F	1. Essential hypertension 2. Normal heart	4/26/39, 150/100 5/17/39, 130/100 8/17/39 12/ 7/39, 142/ 90 4/26/40 7/ 2/40, 146/ 96 10/10/40, 140/100	Roentgen evidence of pulmonary fibrosis in left lung
9. Cancer of left breast	A. D. ..... May 1938: breast, anterior and lateral; supraclavicular space, anterior and posterior; axilla—2,100 r each. October 1938: radical mastectomy	55	F	Normal heart	5/17/38, 132/ 80 6/27/38, 112/ 70 9/24/38, 104/ 70	.....
10. Cancer of left breast	G. S. ..... July 1938: mastectomy. November 1938: left axilla and left supraclavicular space, 1,800 r each; anterior wall of chest, low voltage, 1,200 r	64	F	1. Hypertension, arteriosclerosis 2. Myocardial fibrosis, cardiac enlargement 3. Left bundle branch block 4. Functional capacity I	7/26/38, 132/ 90 11/17/38, 142/ 84 12/15/38, 148/ 80 2/ 2/39, 160/110 5/ 9/39, 150/100 7/14/39 10/24/39 1/26/40, 150/ 90 4/16/40, 134/ 80	Exertion and palpitation unchanged throughout period of observation
11. Cancer of left breast	V. L. ..... April and May 1939: breast, lateral, medial and direct; axilla; supraclavicular space, anterior and posterior—2,100 r each. February 1940: left breast, medial, lateral and inferior, 900 r each	66	F	1. Rheumatic fever, arteriosclerosis 2. Cardiac enlargement, mitral insufficiency 3. Regular sinus rhythm with premature ventricular contractions 4. Functional capacity I	3/14/39, 148/ 80 4/13/39, 160/ 80 6/ 7/39 7/ 3/39 10/23/39 2/ 5/40 4/25/40 10/10/40, 140/ 80	Roentgen evidence of pulmonary fibrosis in left lung
12. Cancer of left breast	G. K. ..... May-June 1938: breast, direct, and supraclavicular space, 2,000 r each; axilla, 1,500 r	28	F	Normal heart	4/18/38, 134/ 68 9/ 6/38	.....
13. Cancer of left breast	T. W. ..... April 1939: supraclavicular space, anterior, posterior and axilla, 1,800 r each (high voltage)	36	F	Normal heart	3/23/39, 118/ 80 5/ 9/39, 108/ 72	.....
14. Cancer of left breast	T. B. ..... June and July 1938: breast, direct, 2,400 r; axilla, anterior, posterior and direct, 2,100 r each; left wall of chest, lateral, 3,100 r	65	F	1. Hypertension, arteriosclerosis 2. Cardiac enlargement, myocardial fibrosis, mitral incompetence 3. Auricular fibrillation 4. Functional capacity II	6/ 2/38, 132/ 80 7/11/38, 112/ 70 8/ 8/38, 104/ 70	Palpitation and dyspnea unchanged
15. Cancer of left breast	T. W. ..... December 1939: axilla, direct, and supraclavicular space, 1,800 r each; anterior wall of chest, 1,500 r (low voltage)	44	F	Normal heart	12/ 6/39, 140/ 80 1/ 3/40, 144/ 80 4/ 2/40, 140/ 80 6/26/40, 118/ 70 10/26/40, 138/ 94	.....

* See table 1 for key to table.

TABLE 3C.—*Data on Patients in Group 3: Mediastinum* *

Diagnosis	Name and Treatment	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Dose Delivered to Heart	Comment
1. Mesothelioma of pleura, left side	S. K. April 1938: mediastinum, anterior and posterior, 600 r each. December 1938: mediastinum, anterior and posterior, 1,200 r each; 10 cm. cone at 70 cm.	42	F	Normal heart	4/ 4/38, 138 80 4/25/38 12/ 2/38, 118/ 80 12/20/38, 140/ 82 1/13/39, 140/ 82	900 r	Persistent cough and dyspnea
2. Tuberculosis of hilar nodes	J. H. April-June 1938: mediastinum, anterior, 1,000 r; mediastinum, posterior, 1,100 r; portal 11 × 14 cm.	27	F	Normal heart	5/ 6/38, 112/ 84 5/25/38, 106/ 78 1/19/39, 128/ 82	750 r	Pregnant 7 months
3. Cancer of esophagus	E. P. Two parasternal and two paravertebral portals, 14 × 17 cm., 1,600 r each, at 70 cm.	51	F	Normal heart	11/ 1/38, 160/ 80 11/26/38, 110/ 90	2,000 r	Marked cachexia and anemia
4. Hodgkin's disease	I. K. June through August 1938: mediastinum, 1,800 r by 4, each portal 4 × 6 cm.; right and left side of neck, 2,400 r each; left axilla, 2,400 r. January 1939: epigastrium, anterior, 600 r, portal 10 × 10 cm. February 1940: spleen, anterior, 600 r, portal 8 × 10	26	F	Normal heart	6/14/38, 128/ 80 9/27/38, 114/ 80 4/30/39, 134/ 90 10/ 2/40, 130/ 80	1,000 r	.....
5. Cancer of esophagus	E. F. 2,500 r by 4 (2 parasternal and 2 paravertebral portals), 1,000 kv. machine, 14 × 7 cm. portals at 70 cm.	67	M	1. Arteriosclerosis 2. Cardiac enlargement, mitral incompetence 3. Regular sinus rhythm 4. Functional capacity I	12/15/39, 148/ 80 12/28/39, 130/100 1/25/40, 118/ 80 2/ 3/40, 128/ 86 3/14/40, 128/ 90 4/11/40, 130/100 5/23/40, 150/100 10/ 3/40, 130/ 90	4,300 r	Bilateral hilar radiation pneumonitis
6. Cancer of esophagus	T. M. 3,000 r by 4 (through 2 parasternal and 2 paravertebral portals), 1,000 kv. machine, 14 × 7 cm. at 70 cm.	71	M	1. Arteriosclerosis 2. Cardiac enlargement, mitral incompetence, myocardial fibrosis 3. Left heart block 4. Functional capacity II	5/ 9/40, 134/ 80 6/23/40, 130/ 90 7/10/40, 110/ 60 8/ 5/40, 130/ 90 10/ 3/40, 130/ 80	5,200 r	Cachectic, bronchopneumonia, mediastinitis
7. Cancer of esophagus	C. G. 1,250 r through each of 4 portals, 14 × 7 cm., at 70 cm.	57	M	Normal heart	11/17/39, 100/ 74 11/28/39, 116/ 70	2,150 r	Died: mediastinitis
8. Cancer of cardiac end of stomach and esophagus	Dr. T. 2,800 r through each of 4 portals, 2 anterior and 2 posterior, 200 kv. at 60 cm.	58	M	Normal heart	10/ 6/38, 80/ 62 12/15/38, 96/ 68	3,100 r	Mediastinitis

9. Cancer of cardiac end of stomach	G. C. ..... Epigastrium, anterior and lateral, 12 × 12 cm., 2,250 r each; epigastrium, posterior, 2,100 r, 200 kv. at 60 cm.	56	M	Normal heart	7/18/38, 120/ 80 8/18/38, 112/ 20 10/ 6/38, 132/ 90	1,600 r	.....
10. Cancer of hilus of right lung	I. C. ..... May 1939: mediastinum, anterior and posterior, 2,200 r each, 10 cm. cone at 60 cm.	73	M	1. Hypertension, arteriosclerosis 2. Myocardial fibrosis, cardiac enlargement 3. Auricular fibrillation 4. Functional capacity I	4/ 4/39, 160/ 98 4/21/39, 160/110 6/29/39, 170/110	1,350 r	Recovered; auricular fibrillation
11. Metastatic teratoma of hilus of left lung	H. R. ..... Mediastinum, anterior and posterior, 80,000 mg. hr. each	39	M	1. Arteriosclerosis 2. Coronary sclerosis 3. Regular sinus rhythm, anginal syndrome 4. Functional capacity II	9/28/35, 138/ 98 12/30/37, 130/ 90 9/30/38, 132/ 90	1,200 r	Died; acute coronary occlusion
12. Cancer of hilus of left lung	C. C. ..... December 1938: mediastinum, anterior and posterior, 10 cm., 3,000 r each. August 1939: mediastinum, anterior and posterior, 8 cm., 1,500 r each; 200 kv. at 70 cm.	57	M	Normal heart	12/ 1/38, 142/ 80 12/30/38, 112/ 70 1/13/39, 98/ 70 3/23/39, 120/ 80 7/11/39, 134/ 90 11/30/39, 130/ 90	2,100 r	Mediastinal pleuritis
13. Cancer of hilus of left lung	W. R. ..... Mediastinum, anterior and posterior, 3,600 r each; lateral wall of chest, 2,400 r; portals 14 × 9 cm.; 200 kv. at 70 cm.	58	M	Normal heart	12/ 1/38, 116/ 78 1/ 5/39, 108/ 80	2,000 r	.....
14. Cancer of lower lobe of left lung	B. L. ..... June 1938: mediastinum, anterior and posterior, 3,000 r each, 200 kv. at 70 cm.	57	M	1. Hypertension, arteriosclerosis 2. Myocardial fibrosis 3. Regular sinus rhythm 4. Functional capacity I	5/26/38, 180/130 8/18/38, 142/ 98	1,500 r	Paralysis agitans
15. Cancer of lower lobe of left lung	H. P. ..... April and May 1938: mediastinum, anterior and posterior, 2,250 r each, portals 10 × 6 cm., 200 kv. at 50 cm.	62	M	Normal heart	4/11/38, 138/ 72 5/18/38 10/ 4/38, 140/ 92 2/17/39, 130/ 90 8/ 2/39, 120/ 80	1,100 r	Two attacks paroxysmal auricular tachycardia; later paroxysmal auricular fibrillation
16. Cancer of lower lobe of left lung	A. S. ..... Mediastinum, anterior and posterior, 3,000 r each, 1,000 kv. machine, 13 cm. cone	54	M	Normal heart	10/10/39, 120/ 90 10/16/39, 100/ 60 10/24/39, 92/ 68 10/31/39, 92/ 64 11/17/39, 90/ 68	2,450 r	.....
17. Cancer of lower lobe of left lung	J. K. ..... Mediastinum, anterior and posterior, 3,000 r each, at 70 cm., 200 kv., 10 cm. cone	62	M	Normal heart	4/12/38, 160/ 80 5/17/38, 130/ 80	2,100 r	.....

* See table 1 for key to table.

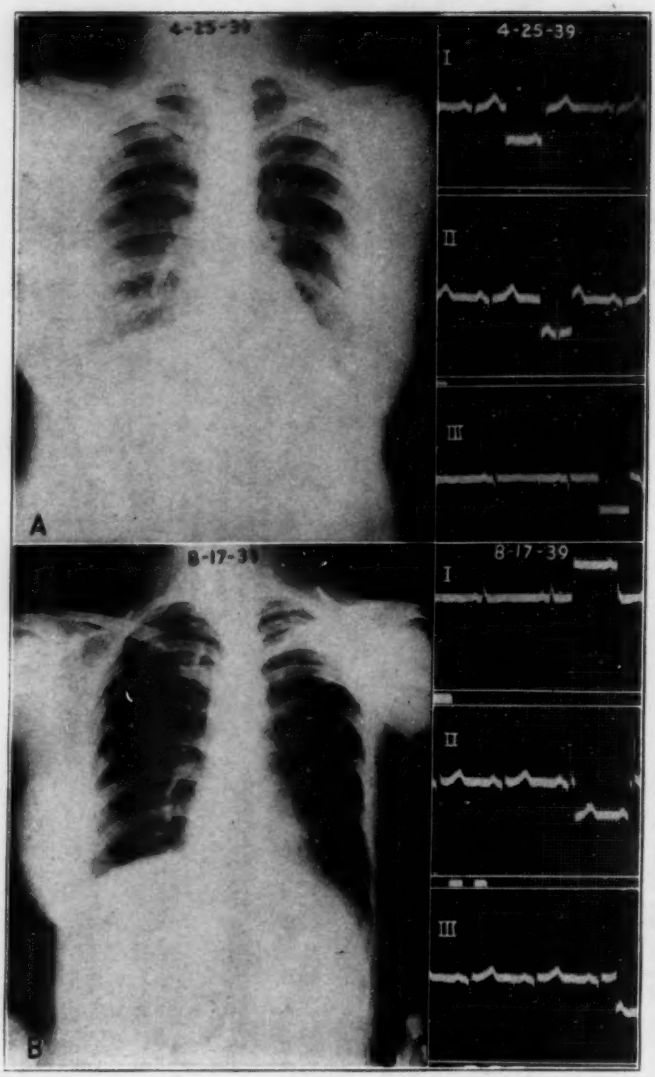
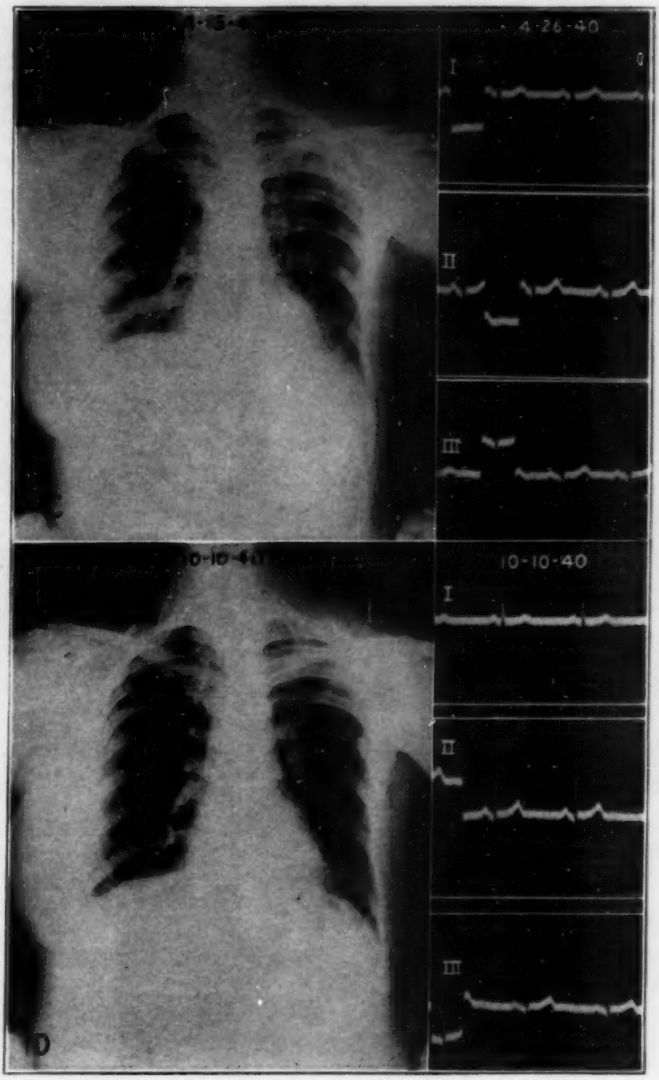


Fig. 2.—*A*. Before treatment: A roentgenogram of the chest and an electrocardiogram of L. L., a woman aged 43 with cancer of the left breast.

B. After roentgen therapy and radical mastectomy: Note the radiation pleuropulmonitis in the upper part of the left lung. T_1 is almost isoelectric, and T_3 has increased voltage.



C. Twelve months after roentgen therapy: The radiation pleuropulmonitis persists but has decreased. T_1 has increased and T_3 has decreased voltage.

D. Eighteen months after treatment: The radiation fibrosis persists. This patient had no cardiac or pulmonary symptoms at any time.

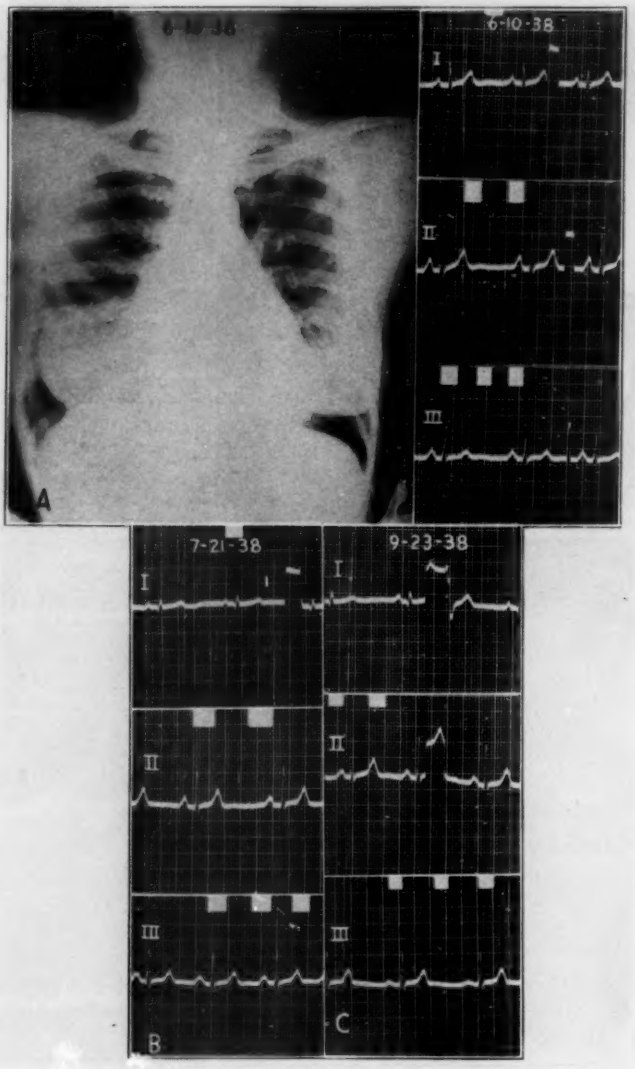


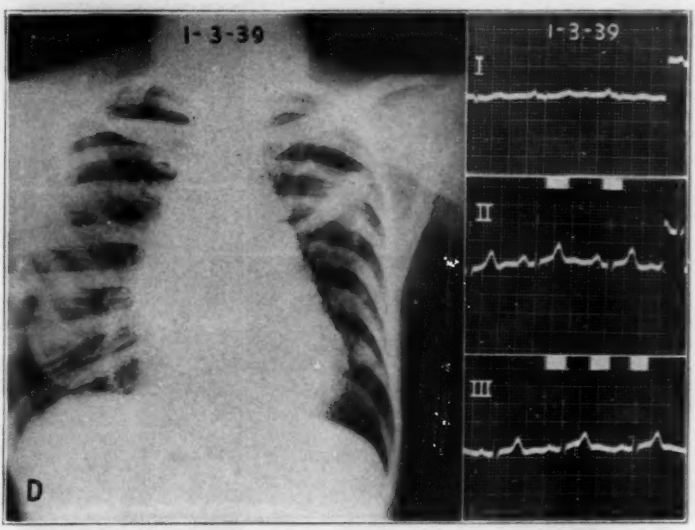
Fig. 3.—*A*. Before treatment: A roentgenogram of the chest and an electrocardiogram of R. W., a woman aged 37 with cancer of the left breast and rheumatic heart disease.

B. After mastectomy: Note the marked decrease of T_1 and the increase of T_3. There were no cardiac or pulmonary complications before or after operation.

C. Immediately after roentgen therapy.

The second patient at the time of writing is a woman aged 45 who was treated for cancer of the left breast six years ago. A severe form of radiation fibrosis of the lung and radionecrosis of the anterior portion of the ribs and overlying skin on the left side developed, which is progressing. Three years ago she began to complain of increasing dyspnea, edema of dependent parts and ascites. At present she has all the classic signs of constricting pericarditis and signs of chronic radiation pleuropulmonitis of the lower lobe of the left lung. The venous pressure is markedly elevated. A biopsy of her liver done two years ago showed "cardiac cirrhosis." A kymogram shows markedly decreased pulsations of both the left and the right side of the heart.

The third patient is a woman aged 35 who also received heavy irradiation of the left side of the chest for cancer of the breast and in whom a severe degree of pulmonary fibrosis developed. Necrosis of the soft tissue of the anterior aspect of the thorax on the left side and of the subjacent ribs developed, and a low grade infec-



D. Seven months after roentgen therapy; four months after operation: T_1 is almost isoelectric. Note the radiation fibrosis in the upper part of the left lung. The patient complained of some dyspnea and cough.

tion of the left lung occurred later. Her complaints since then have been largely dyspnea, cough, expectoration and occasional hemoptysis. The pulsations of the heart on the left side cannot be detected fluoroscopically, either because they are so small in amplitude or because the left lung is too dense. A kymogram, while not conclusive, is strongly suggestive of pleuropericardial adhesions on the left side. To date she has never experienced cardiac failure. Her electrocardiogram shows isoelectric T waves in all leads. This may be due to myocardial degeneration but is probably due to pericardial adhesions.

All these patients are similar in that they received heavy roentgen radiation and chronic infection of the thoracic wall, ribs and left lung developed. As the infection progressed by contiguity, the pericardium was invaded. One can assume either that the pericarditis was caused primarily by roentgen therapy or that the

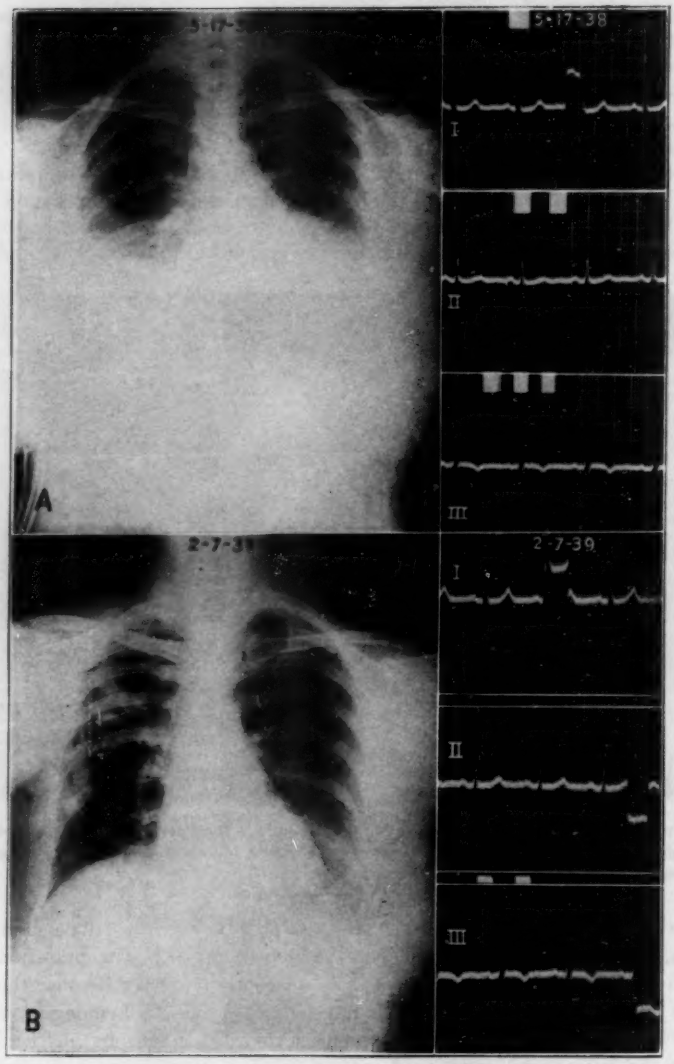
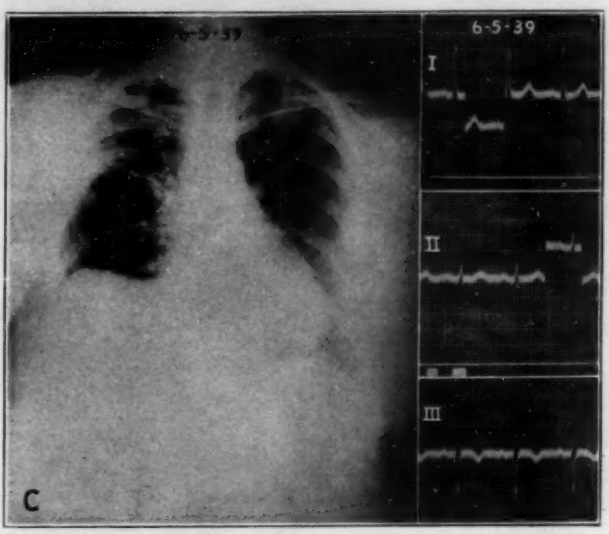


Fig. 4.—*A*. Before treatment: A roentgenogram of the chest and an electrocardiogram of A. W., a woman aged 65 with cancer of the right breast.

B. Eight months after mastectomy and two courses of roentgen treatment: Note the radiation pleuropulmonitis in the upper half of the right lung. In the electrocardiogram T_1 and T_2 have increased and T_3 has decreased voltage.

therapy started a chain of events and the secondary infection was the real cause of the pericarditis. The latter explanation seems more likely.

One patient with teratoma with bulky metastases in the upper left portion of the mediastinum and the left supraclavicular space was treated heavily with radium pack (80,000 milligram hours at 10 cm.) in 1936. The upper portion of the heart was included in the beam of radiation. For a few years prior to this he had complained of vague symptoms suggestive of coronary insufficiency with angina of effort. In 1938 he had well marked symptoms of coronary insufficiency. In 1939 he died suddenly in an attack that was reported to be typical of coronary occlusion. At autopsy the heart showed marked fibrosis, but the endocardium and the pericardium were normal. The degree of coronary arteriosclerosis present did not differ in any way from that seen in a patient who had not had radiation therapy. There was nothing on gross or microscopic examination to suggest any peculiar effect of the gamma rays on the heart.



C. Twelve months after mastectomy: The roentgenogram was made after a third course of roentgen therapy to the right wall of the chest. The right hemidiaphragm has ascended, and the pleuropulmonitis has increased. The electrocardiogram is unchanged.

Arrythmia.—Of the 85 patients studied, 10 had different types of arrythmia before, during or after treatment. One patient with rheumatic heart disease had premature auricular contractions all during the period of observation. One patient with coronary sclerosis and myocardial fibrosis had premature ventricular contractions all during the follow-up period. The contractions were unchanged in frequency. One patient had premature ventricular contractions after being treated for carcinoma of the cardiac end of the stomach with extension up into the esophagus. This occurred at a time when there was a question of a low grade inferior posterior mediastinitis due to extension of esophageal infection. Whether this was a factor in producing the premature contractions is problematic, since many patients with lower mediastinitis have been observed in the hospital and cardiac arrythmia has not been unusually frequent.

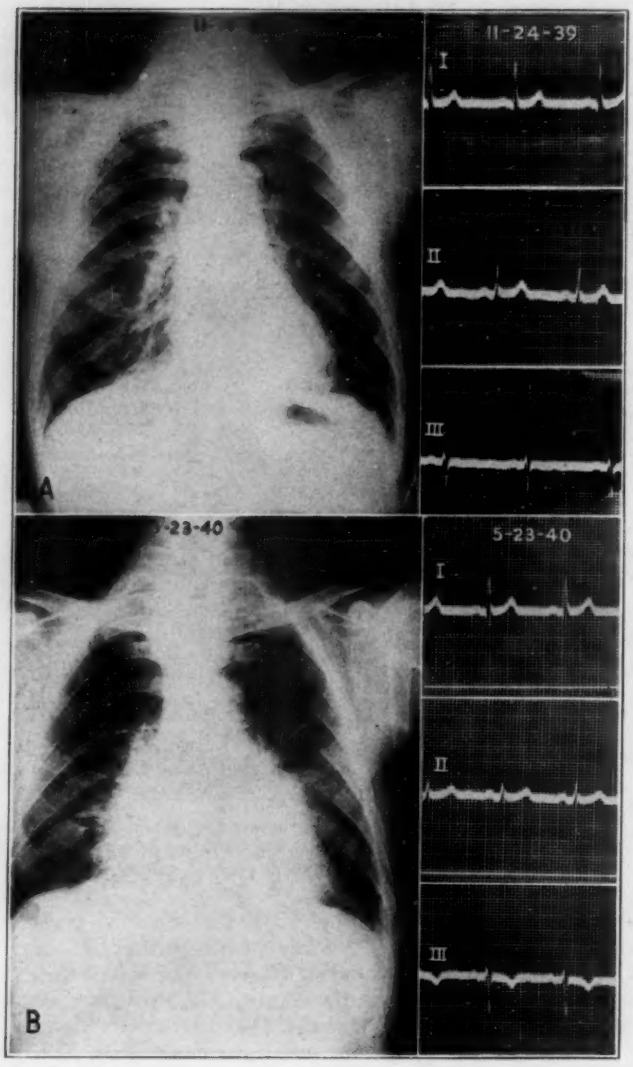
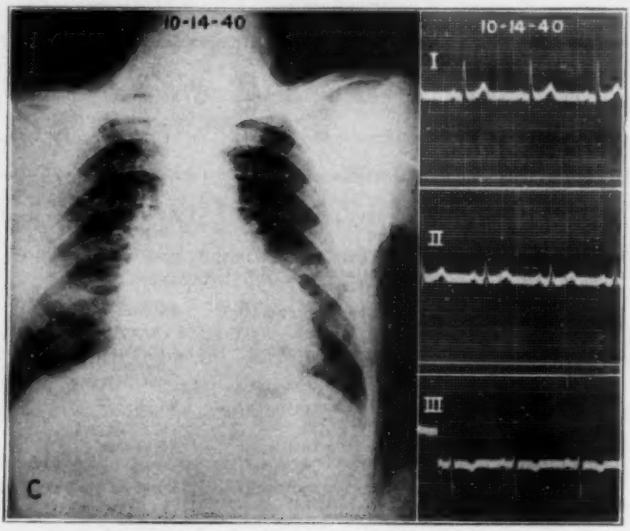


Fig. 5.—*A*. Before treatment: A roentgenogram of the chest and an electrocardiogram of E. F., a man aged 67 with cancer of the esophagus.

B. After roentgen treatment: Intensive roentgen therapy with a 1,000 kilovolt machine had been given. Note the marked degree of radiation pleuropulmonitis. T_1 has increased and T_2 and T_3 decreased voltage. The patient complained of slight dyspnea on exertion and cough.

Three patients with heart disease had auricular fibrillation before treatment. The fibrillation persisted during and after therapy and responded to the usual amount of digitalis. Their management was not more difficult than if radiation had not been given.

One patient had two attacks of paroxysmal auricular tachycardia, one during treatment and one many months after treatment. He was treated for both attacks by his local physician with digitalis, and regular sinus rhythm was restored in twenty-four and forty-eight hours, respectively. This same patient had an attack of auricular fibrillation shortly after paralysis of the left vocal cord developed as a result of extension or metastasis of a carcinoma of the left main bronchus to the hilar region with interruption of the recurrent laryngeal nerve. This was again treated by digitalization, and regular rhythm was restored. The paralysis of the left vocal cord persisted until death.



C. Eleven months after treatment: Radiation pleuropulmonitis persists. T_3 shows slightly increased voltage. At this time the patient was free of pulmonary symptoms and was gaining weight and strength.

One patient had a left bundle branch block before treatment. This persisted unaltered all during the post-treatment period. One patient had a first degree heart block and received heavy radiation directly through the entire heart by four ports. An electrocardiogram taken one day before death showed a reduction of the PR interval from twenty-four hundredths to two tenths of a second.

COMMENT AND SUMMARY

There were two possible ways in which these patients might have been grouped for study. One was to separate those that had heart disease from those with normal hearts and compare the effect of radiation in each group. The other way, as was done here, was to group them on the basis of the region of the body irradiated. From the results that have been obtained it seems that the effect, if any, depends on

the location and treatment of the cancer rather than on the presence or absence of antecedent heart disease.

It is undoubtedly true that the changes in the blood pressure during and after treatment depend on (1) depressive effect of the radiation itself, (2) fever, (3) toxemia, (4) infection, (5) anemia and (6) cachexia. A factor that is probably just as important as all of these other agents is nutrition.

In the patients with cancer of the head and neck in whom dysphagia interfered with ingestion of food the fall in blood pressure was striking. As soon as the dysphagia disappeared and proper feeding was established, the blood pressure rose again. Three patients who had esophageal obstruction relieved by gastrostomy before roentgen treatment was instituted had an increased blood pressure during and after the time they received roentgen therapy. Apparently this was also due to increased intake of food.

TABLE 4.—*Types of Cardiac Arrythmia Observed*

Patient	Sex	Before Therapy	After Therapy	Comment
1	F	Premature auricular contraction	Premature auricular contraction	No change
2	M	Auricular fibrillation	Auricular fibrillation	No change; usual response to digitalis
3	F	Auricular fibrillation	Auricular fibrillation	No change; usual response to digitalis
4	M	Auricular fibrillation	Auricular fibrillation	No change; usual response to digitalis
5	M	0	Paroxysmal tachycardia, 2 attacks; auricular fibrillation	Both attacks subsided
6	F	Left bundle branch block	Left bundle branch block	No change
7	M	Complete heart block, 1st degree	Complete heart block, 1st degree	Auriculoventricular conduction time reduced from 0.24 to 0.20 second one day before death
8	M	Premature ventricular contraction	Premature ventricular contraction	No change
9	F	Premature ventricular contraction	Premature ventricular contraction	No change
10	M	0	Premature ventricular contraction	Posterior mediastinitis ?

The fall of blood pressure in patients who received roentgen radiation directly through the heart for treatment of pulmonary cancer was not as striking as that in the patients with cancer of the head and neck.

Those patients who had cardiovascular complications have already been discussed in the respective groups. In summary there was no evidence that roentgen therapy per se caused the complications that arose. Those with pericarditis and those with the carotid sinus syndrome had a particular set of conditions arising from both the treatment and the disease itself. In the patients with the carotid sinus syndrome it was probably infection and metastases in the cervical nodes plus treatment. In the patients with pericarditis it was radiation pneumonitis plus secondary infection. In these last patients infection seemed to play the major part in the complications produced.

Physical Signs and Symptoms.—It was extremely difficult at times to evaluate the symptoms and signs in patients who had radiation to the thorax. This was particularly true in patients who had radical mastectomy, especially if the operation was for cancer of the left breast. There were two distinct reasons for this difficulty.

One concerned the radiation and one the operation. In many patients both factors were present. Certain events frequently take place in the thorax when the structures within are irradiated. At first acute radiation pleuropulmonitis may develop. If severe enough this may progress to the chronic form of the disease with permanent displacement of the heart toward the affected side, decreased mobility of the diaphragm and in many instances partial fixation of the wall of the chest due to fibrosis of the parietes.

This deformation of the lungs, the mediastinum and the wall of the chest gives rise to (1) dyspnea, (2) cough, (3) pleural pain, (4) occasional hemoptysis and (5) reduced vital capacity.

The dyspnea has certain qualities that distinguish it from cardiac dyspnea. It varies with weather conditions, increases only with effort and often changes little quantitatively over a long period. When it is severe, it is almost always accompanied by cough. There is never any edema or increased pressure in the peripheral veins unless there is complicating mediastinal fibrosis, marked mediastinal distortion or heart disease with congestive failure.

The cough is either dry or productive of scant white mucus. It occurs in paroxysms and is usually worse on arising, on retiring and during exercise. Hemoptysis is infrequent, and when it occurs is almost always preceded by severe paroxysms of cough.

As a result of the displacement of the mediastinum and partial immobilization of the diaphragm and wall of the chest, physical signs elicited on examination are sometimes unusual. The heart may appear to be enlarged to the left. The apical impulse is unusually forceful and may simulate a systolic thrill. Murmurs when present before may be exaggerated or otherwise altered. The pulmonic second sound is often relatively accentuated.

The symptoms and signs may cause the physician to wonder if he is dealing with an induced form of heart disease. With the exception of the 3 patients with pericarditis, whose cases are special instances, there has been no clinical evidence of organic cardiac disorder consequent to radiation therapy. This observation is supported by additional clinical data obtained from the study of over 75 patients with long-standing radiation fibrosis of the lung. In none of these has there been evidence of heart disease provoked by the roentgen therapy.

The vital capacity of the patients who had radiation to the thorax was almost always reduced. This was because of (1) pneumonitis, (2) mediastinal displacement, (3) impaired motion of the diaphragm and (4) immobility of a portion of the thoracic wall. The reduction was temporary if the pneumonitis was mild, recovery complete and the other factors nonoperative. If the pneumonitis became chronic, mediastinal displacement permanent and fixation of the parieties persistent, the vital capacity remained lowered.

Contrary to Gendreau's observations, cardiac arrythmia occurring as a result of roentgen treatment has been infrequent in these patients. One patient in whom premature ventricular contractions developed apparently had a low grade posterior inferior mediastinitis. This may have been a cause for the ectopic beats. The other patient, who had two attacks of paroxysmal auricular tachycardia, was interesting in that the first occurred during treatment and the second many months after treatment was stopped. The tachycardia may have been due to the therapy itself, but it may also have been due to hilar metastasis, since shortly after the second attack he had attacks of paroxysmal auricular fibrillation, and coincidentally with this palsy referable to involvement of the left recurrent nerve developed. From the roentgenograms it was impossible to tell how extensive the disease in the

hilar region was. One can only surmise that involvement of the left vagus nerve or even invasion of the auricular myocardium by neoplastic disease may have been the cause of the fibrillation.

Electrocardiographic Changes.—There has been a large number of papers reporting the changes in the electrocardiograms as a result of altering either the position of the leads in relation to the heart or the relation of the heart to the thoracic cavity. Notable among these have been the observations published by Einthoven,[11] Katz and associates,[12] Kountz and co-workers,[13] Meek and Wilson [14] and many others.[15] In these reports, however, the emphasis has been placed on the variations of the QRS complexes as the position of the heart was changed or as one or more of the cardiac chambers increased in size. Some mention has been made of changes in the configuration of the T waves, but no special reference or explanation relative to them was made.

From a study of the serial electrocardiograms of these patients two general types of variations can be seen. One is the minor variation of all the waves, more marked in some than in others, that occurred in all of the patients. Since this type was present in patients both with and without heart disease, the only logical explanation is that it represented the reaction of the myocardium to infection, toxemia, altered nutrition, general effect of the roentgen rays, anemia or the neoplastic disease itself. In some patients only a few of these factors were important; in others all might have played a part.

The other type of variation was that seen in the patients who had radiation directed to the thorax. While there were some variations in P, Q, R and S waves in the electrocardiograms, they were extremely wide and unpredictable. The T wave changes were consistent, and in many instances one could forecast the alteration that took place. These changes were present in patients with and without heart disease and were most marked when the patient received radiation for cancer of the breast and when there was appreciable evidence both on physical examination and in roentgenograms that radiation fibrosis of the lung with some mediastinal displacement was present. They were less striking when the heart itself was irradiated (see figures 2 through 5).

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11. Einthoven, W.; Fahr, G., and de Waart, A.: Ueber die Aichtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275-315, 1913.

12. Katz, L. N., and Korey, H.: The Manner in Which Electric Currents Generated by the Heart Are Conducted Away, Am. J. Physiol. **111**:83-90 (Feb.) 1935. Katz, L. N., and Rabinow, M.: Appearance of the Electrocardiogram in Relation of the Position of the Heart Within the Chest, Am. J. M. Sc. **192**: 556-559 (Oct.) 1936. Katz, L. N.; Sigman, E.; Gutman, I., and Ocko, F. H.: Effect of Good Electrical Conductors Introduced Near the Heart on the Electrocardiogram, Am. J. Physiol. **116**:343-348 (July) 1936.

13. Kountz, W. B.; Prinzmetal, M.; Pearson, E. F., and Koenig, K. F.: Effect of Position of the Heart on the Electrocardiogram: The Electrocardiogram in Revived Perfused Human Hearts in Normal Position, Am. Heart J. **10**:605-613 (June) 1935.

14. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the Q-R-S Complex of the Electrocardiogram, Arch. Int. Med. **36**:614-627 (Nov.) 1925.

15. Treiger, I., and Lundy, C. J.: Correlation of Shifting Electrical Axis of the Heart with X-Ray Observations in Artificial Pneumothorax, Am. Rev. Tuberc. **29**:546-557 (May) 1934. Boden, E., and Neukrich, P.: Elektrokardiographische Studien am isolierten Säugetier und Menschenherzen bei direkter und indirekter Ableitung, Arch. f. d. ges. Physiol. **171**: 146-191, 1918. Cohn, A. E., and Raisbeck, M. J.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, Heart **9**:311-326 (Dec.) 1922. Cohn, A. E.: On the Relation of the Position of the Enlarged Heart to the Electrocardiogram, ibid. **9**:331-346 (Dec.) 1922.

It is probable that another cause for the T wave changes is the fixation of the thoracic wall. Evidence supporting this is the fact that similar changes have been observed in the electrocardiograms of patients after radical mastectomy, before radiation therapy was started (fig. 3). There was such a patient in this series, and since this patient was seen, others have been observed. The changes are likely to be more marked when mastectomy has been done on the left side. One possible explanation is that there may be an appreciable degree of compensatory emphysema of the contralateral lung when the homolateral lung is partially fixed or compressed by a partially rigid thoracic wall. With these changes there would be a relative shift of the mediastinum toward the affected side.

It seems quite certain that the electrocardiographic changes observed cannot be caused by heart disease. They are present to a lesser degree in the great majority of the patients operated on for cancer of the breast as a result of the mastectomy alone. These changes are not supported by symptoms and signs of heart disease.

Unfortunately, there are not adequate data from postmortem examinations on these patients to tell exactly what type of displacement of the heart occurs as a result of this form of treatment. Probably both displacement of the heart as a whole and rotation of the heart cause these changes. From the experimental work previously done to produce electrocardiographic changes and because of the lack of consistent QRS changes, one cannot even theorize as to the altered conditions in the thoracic cavities of these patients with any degree of accuracy. It must be sufficient for the present to say that there is obviously some altered relation of the heart to the wall of the chest, the diaphragm and the posterior muscle mass and that the conduction of the action current from the heart to these structures, on which the configuration of the electrocardiogram depends, has been changed.

CONCLUSIONS

1. From a study of 84 patients with various types of neoplasms and 1 with tuberculosis of mediastinal lymph nodes who were carefully observed to determine the effect of roentgen therapy on the heart there is no evidence that the heart is affected by roentgen radiation as used at present.

2. The depression of the blood pressure during and after roentgen therapy is probably due to (1) insufficient nourishment, (2) anemia, (3) fever, (4) neoplastic toxemia, (5) general radiation effect and (6) possibly absorption of split protein products.

3. A carotid sinus syndrome may be induced by cervical metastatic disease and will respond to the usual therapy.

4. Adhesive or constrictive pericarditis may occur following severe radiation pleuropulmonitis complicated by infection.

5. Cardiac arrythmia when present may be expected to respond to the usual therapy.

6. A sequence of changes is observed in electrocardiograms made before, during and after roentgen therapy.

CLINICAL SIGNIFICANCE OF GLYCOGEN CONTENT OF LIVER

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The importance of the concentration of glycogen in the liver in patients suffering from a variety of clinical disturbances is generally acknowledged. In some instances glycogen impoverishment plays a greater role than in others, but in no case is a glycogen-poor liver without clinical significance, for there is no question that glycogen is one of the organism's greatest assets and that when impoverishment of this substance occurs a great liability results. It is thus obvious that a measure of the hepatic glycogen may be of real clinical significance. However, methods for quantitative measurement of glycogen in vivo still do not exist.

The purpose of this paper is to present an indirect procedure for the quantitative estimation of hepatic glycogen "reserve" and to indicate the significance of data obtained by this method in various clinical states.

There is ample evidence that a diminution of glycogen in the liver is probably the essential stimulus to the onset of ketone formation by that organ. A decrease in the glycogen content of the liver means that the amount of carbohydrate available for oxidation by the liver is reduced. There is thus a deficient amount of carbohydrate available for the energy requirements of the organ itself. Since the liver is much more active than any other tissue in the body, it must obtain energy from some source other than carbohydrate, and it begins to use protein and fat. Hence a compensatory acceleration in the breakdown of fat and protein occurs. This increased breakdown of fat and protein then results in formation of ketone bodies and dextrose. Acetone bodies are normal products of fatty acid oxidation in the liver,[1] and they appear in excessive amounts in the blood stream only when their rate of production exceeds their rate of oxidation by the tissues.

It is evident that the rapidity with which a liver may be depleted of glycogen is dependent to a great degree on the amount of glycogen present in that organ. Hence a measure of the ability of the liver to maintain its glycogen store should serve as an index of the rapidity with which acetone body formation may occur. Thus, a determination of hepatic glycogen reserve would serve as a gage of the patient's susceptibility to ketosis.

In 1853 Claude Bernard found that the blood flowing from the liver of a fasting or a meat-fed animal contained sugar, while the blood entering that organ contained none. This led him to conclude that sugar is produced and secreted by the liver. In 1857 Bernard isolated glycogen from the liver, and demonstrated it to be the immediate precursor of the sugar liberated by this organ. Furthermore, he found that glycogen could arise from noncarbohydrate sources. Since that time it has been adequately demonstrated that the liver is the only organ capable of secreting sugar into the circulation and that its ability to maintain the blood sugar level successfully is dependent on its glycogen content. In the normal organism an excessive loss of sugar from the blood stream will stimulate the secretion of sugar by the

Portion of thesis submitted to the Graduate School of the University of Cincinnati in partial fulfilment of the requirements for the degree of Master of Science.

1. Mirsky, I. A.: The Source of the Blood Acetone Resulting from the Administration of the Ketogenic Principle of the Anterior Hypophysis, Am. J. Physiol. **115**:424, 1936.

liver and the blood sugar level will not change significantly.[2] However, if the liver is poor in glycogen it will not be able to compensate adequately for the loss of sugar from the blood stream and hypoglycemia will result. Furthermore, if the liver has a low glycogen content and uses this to compensate for a loss of sugar from the blood, it will become further impoverished and consequently will draw on fat and protein for energy, with the formation of acetone bodies as one of its products. It is thus obvious that when acetone bodies appear in the blood stream the hepatic glycogen has reached a minimal value.

These considerations have enabled a procedure to be devised whereby quantitative measurement of the glycogen content of the liver in man is made possible. If the renal threshold for sugar is lowered by means of administration of phlorhizin, an increased drain on the blood sugar and thereby on the glycogen reserve of the liver is produced. In instances in which the glycogen content is normal the loss of sugar from the blood stream by way of the kidneys produces no significant change in the blood sugar level. On the other hand, in conditions in which the hepatic glycogen content is known to be inadequate the excretion of a similar amount of sugar results in a definite diminution of the blood sugar. In addition to the drop in blood sugar there may develop simultaneously a ketonemia. This serves as an index of hepatic glycogen impoverishment and suggests that the excreted sugar is all that the liver contained.

Phlorhizin is a glucoside extracted from the root cortex of apple, cherry, plum and pear trees. On hydrolysis it yields dextrose and phloretin. When phlorhizin or phloretin is administered parenterally, it gives rise to glycosuria. Phlorhizin produces a temporary inhibition of reabsorption of sugar in the renal tubules and permits the sugar which is constantly being filtered through the glomeruli to be excreted. The excessive loss of sugar in the urine results in a rapid depletion of hepatic glycogen just as occurs in hyperthyroidism and in insulin deficiency. When the hepatic glycogen is depleted in consequence of the loss of sugar from the blood, the oxidation of fat and protein is accelerated and an increased excretion of urinary nitrogen and acetone bodies ensues. If the phlorhizinized animal is fed adequate amounts of carbohydrate, there occur an immediate cessation of ketosis and a decrease in protein metabolism.[3]

PROCEDURE

This report is based on the results obtained in a study of 155 subjects, of whom 89 were children and 66 were adults. They were divided into three classes: (1) normal, healthy persons; (2) patients with diabetes mellitus of various degrees of severity; (3) patients with hepatic disease (alcoholic or toxic hepatitis, cirrhosis, obstructive jaundice, hepatomegaly or metastatic disease of the liver).

With the exception of the children and of the adults suffering from hepatic dysfunction, each of the classes was divided into a group which received pretreatment with carbohydrate the evening before the test was performed, and another which received no pretreatment.

The children were divided into three groups: (1) those receiving pretreatment the evening before the test; (2) those receiving pretreatment early in the morning on the day of the test; (3) those receiving no pretreatment.

All adults suffering from hepatic dysfunction received pretreatment. Diabetic patients were permitted to take insulin up to the day of the test. In no case was insulin administered on the morning on which the test was performed.

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2. Soskin, S.: Muscle Glycogen as a Source of Blood Sugar, Am. J. Physiol. **81**:382, 1927. Soskin, S.; Essex, H. E.; Herrick, J. F., and Mann, F. C.: The Mechanism of Regulation of the Blood Sugar by the Liver, ibid. **124**:558, 1938.

3. Chambers, W. H., and Deuel, H. J., Jr.: Metabolism of Glycerol in Phlorhizin Diabetes, J. Biol. Chem. **65**:21, 1925. Deuel, H. J., Jr.; Ellis, H.; Wilson, C., and Milhorat, A. T.: On the Mechanism of Phlorhizin Diabetes, ibid. **74**:205, 1927. Soskin, S.; Levine, R., and Lehmann, W.: Utilization of Carbohydrate by the Phlorhizinized Dog, Proc. Soc. Exper. Biol. & Med. **39**:442, 1938.

Pretreatment with carbohydrate consisted of oral administration of orange juice and cane sugar in an amount sufficient to furnish 2 Gm. of carbohydrate per kilogram of body weight. In those instances in which pretreatment was given the evening before the test this mixture was taken at 9 p. m. In those in which it was administered on the morning of the test it was given to the subject at 3 a. m.

The procedure was as follows: The subject was given his regular evening meal on the day before the test. No food was allowed that night, with the exception of pretreatment when this was administered. As already mentioned, one group of subjects received carbohydrate at 9 p. m. on the evening before, while another group was given the orange juice–cane sugar mixture at 3 a. m. on the morning of the test. Breakfast was omitted, and no food was permitted during the test, which was begun between 7 and 7:30 a. m. and lasted for six hours; however, water, tea or black coffee with saccharin was allowed ad libitum. A sample of blood was drawn at the beginning and again at the end of the six hour period and was analyzed for sugar content by the Somogyi modification of the Shaffer-Hartmann method and for total ketones by a modification of the Van Slyke and Fitz method. Immediately after drawing of the first blood sample, 1 Gm. of phlorhizin dissolved in tenth-normal sodium hydroxide solution was injected intravenously. The subject then emptied his bladder completely. Since the injected phlorhizin was excreted fairly rapidly, it was found necessary to administer a second 1 Gm. dose of phlorhizin intravenously at the end of three hours in order to maintain an adequate glycosuria. The urine was collected during the six hour period, and the total amount of sugar excreted was determined. As previously stated, a second sample of blood was drawn at the end of the six hour period.

RESULTS

The data obtained in this study are summarized in tables 1 to 5. An analysis of the data may best be made as follows: (1) changes in blood sugar; (2) glycosuria; (3) loss of sugar from the liver; (4) ketosis.

TABLE 1.—*Influence of Phlorhizin on the Hepatic Glycogen Reserves of Normal Adults*

Subject No.	Age	Sex	Weight, Kg.	Initial Blood Sugar, Mg./100 Cc.	Fall in Blood Sugar, Mg./100 Cc.	Dextrose Excreted in Urine, Gm.	Total Decrease in Free Sugar, Mg./Kg.	Loss from Liver, Mg./Kg.	Rise in Blood Ketones, Mg./100 Cc.
Dinner at 6 P. M.; Nothing Thereafter									
16	24	M	82.0	55	11	34.6	33	455	0
39	32	M	76.3	74	1	23.3	3	302	0
2	32	M	76.3	87	14	24.2	42	350	0
7	45	M	45.4	65	15	10.9	45	285	0
8	56	M	71	81	1	17.3	3	241	0
9	41	F	51	58	1	12.5	3	248	0
14	63	F	....	90	9	17.4	..	...	0
15	50	F	....	66	0	17.7	..	...	0
81	29	F	....	84	5	17	..	...	0
Dinner at 6 P. M.; 2 Gm. Carbohydrate per Kg. at 9 P. M.									
94	60	M	45.4	88	6	14.0	18	290	0
68	44	M	74.6	81	7	23.0	21	287	0
32	60	M	66	75	4	14.0	12	200	0
33	60	M	66	74	1	22.3	3	341	0
27	19	M	....	49	7	15.0	..	...	0
34	36	M	....	66	4	21.9	..	...	0
37	49	M	....	63	10	20.4	..	...	0
38	33	M	....	62	18	21.7	..	...	0
44	37	M	....	90	4	26.5	..	...	0
46	40	M	....	99	9	....	..	...	0
50	26	M	....	82	0	28.6	..	...	0
51	27	M	....	76	5	26.0	..	...	0
150	38	M	70.0	88	2	6.4	6	85	0
91	37	F	57.7	87	10	15.5	30	239	0
41	26	F	49.5	61	1	22.0	3	437	0
40	25	F	....	75	6	19.9	..	...	0

1. *Changes in Blood Sugar.*—Table 6 summarizes the findings in the various groups. It is obvious that the administration of carbohydrate to normal adults at 9 p. m. on the evening before had no significant influence on the changes in the

blood sugar consequent to administration of phlorhizin. The average change in the blood sugar is relatively insignificant and within the limits of experimental error.

In the adult diabetic group a pronounced drop in blood sugar level occurred irrespective of whether or not the patients were pretreated with carbohydrate the night before. Thus, whereas in the normal group the blood sugar decreased by 3 per cent after administration of phlorhizin, a decrease of 46 per cent occurred in the diabetic groups.

The findings in normal children differ decidedly from those in adults. Thus the nonpretreated group had a drop of 23 per cent in the blood sugar level consequent to administration of phlorhizin, as compared with a 5 per cent rise in adults. Furthermore, it is of importance to note that the children given carbohydrate at

TABLE 2.—*Influence of Phlorhizin on Hepatic Glycogen Reserves of Diabetic Adults*

Subject No.	Age	Sex	Weight, Kg.	Initial Blood Sugar, Mg./100 Cc.	Fall in Blood Sugar, Mg./100 Cc.	Dextrose Excreted in Urine, Gm.	Total Decrease in Free Sugar, Mg./Kg.	Loss from Liver, Mg./Kg.	Rise in Blood Ketones, Mg./100 Cc.
Dinner at 6 P. M.; Nothing Thereafter									
69	60	M	60.4	151	29	28.0	87	336	0
17	60	M	62.7	42	3	9.6	9	144	0
18	72	M	45.4	162	115	18.5	345	63	17.2
21	63	M	44.5	104	52	21.2	156	333	19.6
19	17	M	....	210	77	42.5	..	...	2.6
24	52	M	....	206	108	33.7	..	...	5.1
31	47	M	....	204	77	43.4	..	...	0
3	68	M	....	259	159	22.4	..	...	13.4
10	62	M	72	160	102	14.5	306	...	0
78	28	F	43.2	89	29	10	87	285	10.5
1	47	F	60	84	29	....	87	...	15.5
Dinner at 6 P. M.; 2 Gm. Carbohydrate per Kg. at 9 P. M.									
67	53	M	48.6	238	202	52.0	606	464	23.5
123	24	M	52.3	93	9	15.8	27	275	0
124	61	M	55.5	231	94	39.5	282	490	0
76	45	F	78.2	141	33	25.0	99	231	0
35	22	F	47.2	194	108	24.9	324	204	6.3
63	62	F	71.1	282	112	21.0	336	41	0
61	52	F	45.5	156	47	23.9	141	385	0
43	51	F	52.3	261	161	37.3	483	230	13.7
45	50	F	56.8	270	171	54.0	513	457	0.8
28	17	F	....	121	79	22.0	..	...	7.1
53	51	F	....	214	117	29.0	..	...	0
54	52	F	....	218	110	28.0	..	...	0

9 p. m. had a smaller decrease in blood sugar, while those given carbohydrate at 3 a. m. had no change.

The diabetic children all had a marked decrease in blood sugar. This decrease is much greater than that observed in the adult diabetic patients. The administration of carbohydrate the night before appears to have only a slight effect in inhibiting the decrease which follows administration of phlorhizin.

These data reveal that the diabetic subjects invariably showed a decrease in blood sugar concentration consequent to administration of phlorhizin. Of interest is the fact that the majority of these patients were under good clinical control as far as their diabetic status was concerned and that nevertheless great differences were noted as compared with the nondiabetic group.

Patients suffering from a variety of hepatic disturbances revealed a drop in blood sugar consequent to administration of phlorhizin even though the initial level was normal. In this respect these patients behaved like normal children.

2. *Glycosuria.*—The excretion of dextrose varies greatly from patient to patient and from group to group. Reference to tables 1 to 5 clearly demonstrates not only that differences in body weight play a role in the variations in sugar excretion but

that age and clinical status are important factors. In view of the many variables which determine the amount of sugar excreted consequent to administration of phlorhizin, no attempt to compare the various groups on the basis of total dextrose excretion will be made. Generalizing, normal adults excreted approximately 25 Gm. in six hours, while normal children excreted approximately 10 Gm. in six hours.

TABLE 3.—*Influence of Phlorhizin on Hepatic Glycogen Reserves of Normal Children*

Subject No.	Age	Sex	Weight, Kg.	Initial Blood Sugar, Mg./100 Cc.	Fall in Blood Sugar, Mg./100 Cc.	Dextrose Excreted in Urine, Gm.	Total Decrease in Free Sugar, Mg./Kg.	Loss from Liver, Mg./Kg.	Rise in Blood Ketones, Mg./100 Cc.
Dinner at 6 P. M.; Nothing Thereafter									
136	14	M	43.6	76	12	17.8	36	372	2.1
137	14	M	54.1	77	3	19.4	9	349	0
138	14	M	50	90	17	23.8	51	425	2
139	13	M	46.8	117	49	22.5	120	361	0
140	13	M	38.2	76	15	14.8	54	333	10.1
141	13	M	40	74	10	14	30	320	0
142	13	M	42.3	88	7	24	21	546	0
143	14	M	47.3	84	12	23.9	36	469	0
78	4	M	14.8	71	14	9	42	566	17.1
80	8	M	25.5	118	55	10	165	227	14.6
83	6	F	18.9	77	13	10	39	490	9.9
85	12	F	52.6	90	23	21	69	323	0.6
86	11.5	F	33.5	80	15	14	45	351	0
87	9	F	28.2	89	24	11	72	492	6.5
74	14	F	67.7	86	25	24	75	290	0
Dinner at 6 P. M.; 2 Gm. Carbohydrate per Kg. at 9 P. M.									
57	13	M	58.2	84	5	21	15	386	0
60	6	M	25	86	11	14	33	527	0
65	11	M	33.6	85	2	15	6	440	0
98	5	M	19.1	84	0	9.6	18	484	7
99	10	M	32.5	87	8	13.2	24	388	0
100	5	M	20.9	90	23	11.3	69	471	8
102	13	M	39.6	90	3	18.5	9	458	2.2
105	14	M	46.8	81	11	15.6	33	304	0
106	13	M	51.4	85	17	23.6	51	408	0
48	19	M	38.6	81	5	15.8	15	425	0
90	4	M	14.7	82	23	15.1	69	958	13.3
114	5	M	16.4	87	18	10.4	54	580	7.4
56	12	F	42.3	78	0	19	0	449	0
89	11	F	33.3	91	3	18.7	9	553	0
96	12	F	45.9	85	7	27.1	21	569	0
97	16	F	50.4	91	9	21.1	27	392	0
101	8	F	25.5	96	20	16.4	60	582	6.1
107	14	F	53.4	70	2	20.6	6	392	0
108	13	F	57.8	73	2	16.3	6	276	3
109	11	F	30	82	18	12.6	54	366	3
110	12	F	32.5	88	15	19.8	45	564	0
112	8	F	21.1	76	22	9.3	66	375	10.6
113	9	F	28.9	82	15	11.8	45	363	0
117	9	F	23.4	90	11	13.4	33	539	0
118	11.5	F	34.2	82	8	16.4	24	456	0
Dinner at 6 P. M.; 2 Gm. Carbohydrate at 3 A. M.									
121	12	M	42.5	49	31	17.5	93	514	0
122	12	M	38	65	13	20.2	39	571	0
125	13	M	37.8	86	13	17.1	39	413	0
126	15	M	49.5	78	0	20	0	444	0
127	10	M	35.6	75	4	18	12	437	0
128	13	M	50.9	85	10	24	30	441	0
129	10	M	31.8	83	9	15.7	27	404	0
130	9	M	30	77	8	15.3	24	486	0
131	9	M	28.4	80	5	13.4	15	457	0
132	9	M	29.1	71	0	13.6	0	467	0
134	14	M	47.7	71	11	21.5	33	434	0
135	13	M	43	68	7	18.6	21	453	0

3. *Loss of Sugar from the Liver.*—Another comparison is permissible. The dextrose that appears in the urine consequent to administration of phlorhizin is excreted from the blood stream. The sugar in the blood stream is in turn secreted by the liver, where it takes origin from the glycogen present in that organ. In order to compute what proportion of the excreted sugar has taken origin from

hepatic glycogen, it is necessary to take into account the over-all changes in the blood sugar.

In instances in which the blood sugar reveals no change, all the sugar that appears in the urine must have come from the liver. On the other hand, if the over-

TABLE 4.—*Influence of Phlorhizin on the Hepatic Glycogen of Diabetic Children*

Subject No.	Age	Sex	Weight, Kg.	Initial Blood Sugar, Mg./100 Cc.	Fall in Blood Sugar, Mg./100 Cc.	Dextrose Excreted in Urine, Gm.	Total Decrease in Free Sugar, Mg./Kg.	Loss from Liver, Mg./Kg.	Rise in Blood Ketones, Mg./100 Cc.
Dinner at 6 P. M.; Nothing Thereafter									
72	16	M	51.4	155	101	23	308	144	3.5
75	6	F	23.6	167	127	11	381	85	10.7
82	10	F	38.6	275	273	37	819	139	2.3
84	12	F	38.4	246	187	39	561	456	6.4
Dinner at 6 P. M.; 2 Gm. Carbohydrate per Kg. at 9 P. M.									
52	16	M	54.5	305	155	63	465	691	0
56	7	M	25.6	448	190	52	576	1,942	15
62	15	M	47.7	318	249	48	747	300	0
70	11	M	32.7	305	178	53	534	1,085	7.3
109	16	M	47.8	234	175	29.6	525	94	0
119	11	M	31.8	306	245	48.1	735	777	7.8
55	15	F	39.5	154	87	39	261	435	0
59	10	F	28.1	248	149	35	447	653	11.5
64	12	F	51	361	233	74	699	1,175	19
98	6	F	....	91	45	10.9	135	223	3.7
49	14	F	....	166	97	24.2	291	182	0
Dinner at 6 P. M.; 2 Gm. Carbohydrate per Kg. at 3 A. M.									
133	16	M	56.4	392	247	98.3	741	1,000	1.7
144	15	M	51	343	259	57.5	777	350	0
146	6	M	20	306	217	24.9	651	594	12.3
149	15	M	41.4	430	318	89.5	954	483	5.7
152	12	M	40	292	153	49.4	459	776	8.1
145	11	F	40	477	382	45.7	1,146	0	0
148	15	F	53.6	461	306	92.3	924	798	6
151	15	F	53.4	552	241	....	....	....	11.2
153	16	F	56.6	346	196	80.4	588	822	0
154	15	F	51.8	381	307	57.1	921	181	0
155	15	F	43.9	415	319	64	957	501	0

TABLE 5.—*Influence of Phlorhizin on the Hepatic Glycogen Reserves of Adults with Hepatic Dysfunction*

Subject No.	Age	Sex	Weight, Kg.	Initial Blood Sugar, Mg./100 Cc.	Fall in Blood Sugar, Mg./100 Cc.	Dextrose Excreted in Urine, Gm.	Total Decrease in Free Sugar, Mg./Kg.	Loss from Liver, Mg./Kg.	Rise in Blood Ketones, Mg./100 Cc.
Dinner at 6 P. M.; 2 Gm. Carbohydrate per Kg. at 9 P. M.									
13	50	M	60	65	6	16.3	18	220	0
20	30	M	56.4	77	54	10	162	207	0
12	39	M	63.1	85	15	18.9	45	255	0
4	46	M	....	107	36	21.6	..	....	8.9
6	41	M	....	82	27	....	..	....	0
115	43	M	73.6	119	28	17	84	147	0
111	19	F	50	81	13	19.1	36	345	0
23	30	F	50	75	30	13.1	90	172	7.7
22	25	F	....	53	21	10.3	..	....	24.5
96	65	M	55.9	89	13	18.3	39	288	0
26	32	M	....	80	31	20.8	..	....	0
29	50	M	....	62	13	7.5	..	....	0
30	46	M	....	65	23	5.4	..	....	0
35	42	M	....	70	18	25.2	..	....	0
147	38	M	68.4	97	14	21.3	42	270	0
42	68	F	51.8	79	13	9.7	29	148	0

all change in blood sugar is a rise, it is obvious that less sugar has appeared in the urine than left the liver. Hence, in order to determine how much sugar left the liver it is necessary to compute the actual amount of sugar causing the rise in blood sugar concentration and to add that to the amount excreted in the urine. If the

over-all change of the blood sugar shows a fall in level, the amount of sugar excreted in the urine is equal to the sum of that secreted by the liver and that coming from the blood in consequence of the decreased concentration of blood sugar.

In order to make these calculations it becomes essential to determine the significance of a change in the blood sugar in terms of the body as a whole. Various values for the mixing volume for distribution of sugar in the body are to be found in the literature. These vary from 18 to 50 per cent of the total body weight. A value of 30 per cent has been found to approximate closest to the true mixing volume (Darrow, 1935; Blatherwick, 1935). With this distribution factor it becomes possible to compute a change in blood sugar in terms of milligrams of dextrose per kilogram of body weight. Thus, for example, the patient in case 2, weighing 76.3 Kg., had a rise of blood sugar of 14 mg. per hundred cubic centimeters at the end of the six hour interval. This was calculated to mean a rise of 0.14 mg. per cubic centimeter of blood, or 42 mg. of dextrose per kilogram of body weight, i. e., 30 per cent of 1 Kg. $\times$ 0.14. Since this patient excreted 24 Gm. of sugar during the experimental period, the excretion in the urine per

TABLE 6.—*Changes in Blood Sugar in the Various Groups*

Group	Pre-treatment	Blood Sugar		
		Initial, Mg. per 100 Cc.	Final, Mg. per 100 Cc.	Per Cent of Change
Normal adults	None	74	77	+ 5
	At 9 p. m.	75	69	— 8
Average		75	73	— 3
Diabetic adults	None	164	93	—43
	At 9 p. m.	210	106	—50
Average		187	100	—46
Normal children	None	86	66	—23
	At 9 p. m.	84	74	—12
	At 3 a. m.	74	75	+ 1
Diabetic children	None	236	64	—73
	At 9 p. m.	272	118	—60
	At 3 a. m.	332	117	—64
Adults with hepatic dysfunction	At 9 p. m.	81	60	—28

kilogram of body weight was 317 mg. In view of the fact that the liver was responsible for the addition to the mixing volume of 42 mg. of dextrose per kilogram, the total loss from the liver was 42 + 317 mg. of sugar per kilogram of body weight. On the other hand, the patient in case 82, weighing 38.6 Kg., showed a drop in blood sugar of 273 mg. per hundred cubic centimeters at the end of the experimental period. This was calculated to mean a drop of 2.73 mg. per cubic centimeter of blood, or 819 mg. per kilogram of body weight, i. e., 30 per cent of 1 Kg. $\times$ 2.73. Since this patient excreted 37 Gm. of sugar during the six hour interval, the excretion in the urine was 958 mg. per kilogram. Thus the secretion of extra sugar by the liver during the experimental period was 958 — 819, or 139, mg. of sugar per kilogram of body weight.

Computing the data as just outlined, it is possible to compare the different groups on the basis of the amount of extra dextrose secreted by the liver during the experimental period (table 7).

It is of importance to emphasize that the figure designated as "loss of sugar from the liver" represents not the total amount of glycogenolysis but merely the additional breakdown consequent to the increased excretion of sugar in the urine. Thus it may be noted that the normal adults secreted from the liver an extra 49 mg. per kilogram of body weight per hour. A similar figure is obtained for the adult

diabetic group. Although both groups secreted the same amount of extra sugar from the liver during the experimental period, only the normal group was able to maintain the blood sugar at its original level; the diabetic group had a decided drop in blood sugar concentration. The obvious implication of this finding is that there was not enough glycogen present in the persons with diabetes to permit adequate maintenance of their blood sugar level. In support of this view are the findings which will be discussed under the heading of ketosis.

Of interest is the observation that the rate of the extra glycogenolysis consequent to the increased glycuresis in the normal children was very rapid as compared with that of normal adults. The livers of the normal nonpretreated children secreted an average of approximately 100 mg. of sugar per kilogram more than the livers of the normal adults during the six hour period. The administration of carbohydrate to children results in a greater availability of glycogen, as is indicated by the fact that glycuresis induces a still greater loss from the liver while the blood sugar tends to fall little or not at all.

TABLE 7.—*Loss of Dextrose from Liver and Development of Ketosis in Various Groups*

Group	Pre-treatment	Loss from Liver, Mg./Kg.	Ketosis, per Cent of Cases
Normal adults	None	315	0
	At 9 p. m.	268	0
Average		292	0
Diabetic adults	None	230	64
	At 9 p. m.	299	41
Average		265	52
Normal children	None	391	53
	At 9 p. m.	468	36
	At 3 a. m.	404	0
Diabetic children	None	206	100
	At 9 p. m.	621	55
	At 3 a. m.	613	55
Adults with hepatic dysfunction	At 9 p. m.	324	19

The diabetic children had a large secretion of extra sugar from the liver. This demonstrates the ease with which it is possible to accelerate glycogenolysis in children.

Patients suffering from hepatic dysfunction likewise had a large secretion of extra sugar from the liver. These findings differ from those for diabetic adults in that here more glycogen is available in the liver and hence the amount of glycogen breakdown is greater.

This method of analysis permits a comparison between the groups. However, the significance of the data becomes apparent only when they are correlated with the changes in blood sugar and the development of ketosis.

4. *Ketosis.*—The data concerning the development of ketosis are detailed in tables 1 to 5. Since, as was pointed out in the introduction, ketosis develops only when the concentration of glycogen in the liver is at a minimum, it is not considered of importance at this point to discuss the actual amounts of ketone bodies developed during the experimental period. For analytic purposes it is of greater interest to determine the percentage of cases in which ketosis developed, since the appearance of 1 mg. of acetone bodies in the blood stream is as significant as is the appearance of a larger amount.

Reference to table 7 reveals that ketosis did not develop in the normal adults even though their hepatic glycogen stores were deprived of the same amount of

sugar as were those of the diabetic adults. Thus, when 292 mg. of sugar per kilogram was removed from the livers of the normal adults ketosis did not develop, whereas after removal of 265 mg. of sugar per kilogram of body weight from the livers of the diabetic adults, ketosis developed in 52 per cent of them.

It is of interest to emphasize the fact that normal children receiving dinner at 6 p. m. and no carbohydrate thereafter not only lost a greater amount of sugar from the liver during the experimental period than did normal adults and showed a fall in blood sugar but also had ketosis. In 53 per cent of the children receiving no pretreatment ketosis developed. On the other hand, when additional carbohydrate was administered at 9 p. m., more glycogen thus being made available, only 36 per cent of these children revealed a ketonemia, while the group as a whole had a greater loss of sugar from the liver and a smaller drop of blood sugar. When

TABLE 8.—*Relation Between Presence of Ketosis and Change in Sugar Content of Blood and of Liver*

Normal adults	Insignificant change in blood sugar No ketosis 293 mg. sugar per kilogram from liver
Diabetic adults	Marked fall in blood sugar Ketosis in 52 per cent of cases 265 mg. sugar per kilogram from liver
Normal children given no pretreatment	Moderate fall in blood sugar Ketosis in 53 per cent of cases 391 mg. sugar per kilogram from liver
Normal children pretreated at 9 p. m.	Slight fall in blood sugar Ketosis in 36 per cent of cases 468 mg. sugar per kilogram from liver
Normal children pretreated at 3 a. m.	No change in blood sugar No ketosis 464 mg. sugar per kilogram from liver
Diabetic children given no pretreatment	Marked drop in blood sugar Ketosis in 100 per cent of cases 206 mg. sugar per kilogram from liver
Diabetic children pretreated	Marked drop in blood sugar Ketosis in 55 per cent of cases 617 mg. sugar per kilogram from liver
Adults with hepatic dysfunction	Marked drop in blood sugar Ketosis in 19 per cent of cases 334 mg. sugar per kilogram from liver

normal children received carbohydrate at 3 a. m., ketosis did not develop, nor was there any drop in blood sugar.

The findings are entirely different in the group of diabetic children. Those who received no extra carbohydrate secreted a relatively smaller amount of dextrose from the liver, and all of them revealed ketosis. The administration of carbohydrate to the diabetic children made available a greater amount of glycogen for subsequent breakdown, as indicated by the loss from the liver, and resulted in a reduction in incidence of ketosis to 55 per cent.

The studies with the adult group suffering from various hepatic dysfunctions reveal that ketosis developed in 19 per cent of the patients at the same time that a drop in blood sugar and an increase in glycogenolysis occurred.

A clearer picture of our findings becomes apparent when the different groups are compared in terms of all the data, as in table 8.

COMMENT

Although opinions differ as to the exact mechanism responsible for the syndrome of diabetes mellitus, unanimity exists with regard to the fact that in

this condition the hepatic glycogen is decreased. When the glycogen falls to a certain minimal level, oxidation of fat is accelerated and ketosis ensues. Since ketosis is the major factor responsible for the development of diabetic coma, it is obvious that any measure of the susceptibility to ketosis can serve also as an index of susceptibility to coma. Since the latter is really the most important single factor indicative of severity of diabetes, it is obvious that the aforementioned "measure" would serve also as an index of diabetic severity.

If excretion of sugar via the kidneys is accelerated, the blood sugar will remain level so long as an adequate amount of glycogen is present in the liver. If an adequate amount of glycogen is not present in that organ, the blood sugar will fall until the rate of hepatic secretion is equal to the rate at which sugar is lost from the blood stream. Thus a measure of the glycogen reserve of the liver may be obtained.

It may be argued that the extra dextrose which is excreted in the urine consequent to administration of phlorhizin may be due to gluconeogenesis. In order to obviate this criticism, an experiment was performed in which the hourly excretion of nitrogen was studied before and after the injection of phlorhizin. No change whatsoever occurred in nitrogen excretion, even though an increased glycuresis took place.

The fact that with the same loss of sugar from the liver ketosis developed in the diabetic adult group but not in the normal adult group suggests strongly that the glycogen reserves of the persons with diabetes were inadequate at the outset of the study. It is apparent that the administration of phlorhizin produces an effect similar to that which any other glycogenolytic agent would induce. That is to say, administration of this glucoside permits one to measure the capacity of the liver to retain carbohydrate in amounts sufficient to prevent ketogenesis and indicates the course of events which might ensue consequent to the development of an infection or other glycogenolytic stimulus.

The clinical consensus is that children are more susceptible to the development of ketosis than are adults. The present study provides quantitative evidence to substantiate this clinical impression. It was found that normal children secrete relatively large amounts of carbohydrate and have a drop in blood sugar and a rise in blood acetone bodies when excretion of sugar is induced. That this is dependent on glycogen reserve is definitely indicated by the fact that in our experiments administration of extra carbohydrate at 9 p. m. or at 3 a. m. resulted in a decreasing ketosis and an inhibition of the tendency toward development of hypoglycemia (tables 6 and 7).

Not only is the glycogenolytic rate greater in the normal child than in the adult, but it is still further increased in the diabetic child, which indicates a still greater susceptibility to ketosis. This may account for the fact that diabetic children are so susceptible to coma and that their diabetic condition is relatively severe. For, starting with an equal concentration of glycogen in the liver, the child will lose this glycogen at a faster rate than the adult, and if diabetes or an infection supervenes, the tendency to ketosis is further augmented.

Of interest is the observation that the younger the child the greater is his susceptibility to ketosis. However, the number of cases available for analysis are too few to permit statistical consideration.

In view of the preceding observations, it may be possible that the methods outlined in this thesis can be utilized for categorizing the severity of diabetes in individual patients, since with a given loss of glycogen from the liver differences in susceptibility to ketosis and in the drop in blood sugar may be noted in these patients. Furthermore, it may be possible to employ this procedure to determine

the presence or absence of latent diabetes. For example, Mrs. N. L., mother of a diabetic child, had a fasting blood sugar of 89 mg. per hundred cubic centimeters and no fasting glycosuria. Six hours after administration of phlorhizin the sugar content of the blood fell to 60 mg. per hundred cubic centimeters and 10.5 mg. of acetone bodies per hundred cubic centimeters appeared. Calculation revealed that 283 mg. per kilogram of extra dextrose was secreted by the liver during the six hour interval. Since a normal patient would secrete a similar amount of sugar without the development of ketosis or hypoglycemia, it is obvious that this patient has a hepatic glycogen impoverishment. Of course it is possible that in such instances one is dealing not with latent diabetes mellitus but with some other hepatic dysfunction. The presence of other stigmas of hepatic dysfunction should determine the diagnosis.

The fact that patients suffering from disturbances of the liver tend to retain relatively small amounts of glycogen is demonstrated in these studies, which also lend support to the evidence obtained in experiments on lower species that glycogenesis and glycogenolysis are disturbed in diseases involving the liver.

SUMMARY AND CONCLUSIONS

Administration of phlorhizin and the consequent glycosuria result in removal of circulating sugar. In conditions in which the glycogen reserve of the liver is adequate the blood sugar remains relatively constant. In conditions in which the glycogen reserve is inadequate the blood sugar level drops and ketosis may develop.

The study reveals that diabetic adults do not retain carbohydrate in their livers to the same degree as do normal adults and that removal of relatively small amounts of sugar from their blood stream results in a further deprivation of liver glycogen, with consequent development of hypoglycemia and ketosis.

Children cannot retain carbohydrate to the same degree as do adults, because of an apparent increased rate of glycogenolysis. This is true not only for diabetic children but for normal children and accounts for their susceptibility to ketosis. Administration of carbohydrate to normal children results in a greater deposition of glycogen in the liver, so that their reserve is increased and their susceptibility to ketosis decreased.

Patients suffering from hepatic dysfunction have an inadequate glycogen reserve.

The possibility is suggested that the method outlined may be of value in categorizing diabetic severity.

Medical Arts Building.

CARDIOVASCULAR MANIFESTATIONS IN PERNICIOUS ANEMIA

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Profound circulatory changes occur in both primary and secondary anemia. With a decrease in the hemoglobin content of the blood the output of the heart is increased.[1] This is the outstanding compensatory mechanism for the loss of oxygen-carrying power of the blood. The cardiac rate is also increased in anemia.[2] Although the cardiac acceleration is moderate, rarely more than 120 per minute, it results in a certain increase in cardiac output. This increase in minute volume output is due, likewise, in part, to lowering of the viscosity of the blood.[1c] Nevertheless, the increased cardiac output observed in anemia is due mainly to the increased systolic output of the heart. This increase in cardiac output is directly proportional to the decrease in hemoglobin content of the blood. A 200 per cent and a 300 per cent increase are reported to occur with hemoglobin levels of 30 per cent and 20 per cent respectively, the cardiac output being normal when the hemoglobin content of the blood is 50 per cent or more.[3]

Reasons for this augmented cardiac output in anemia have been given.[2a] In blood with a 100 per cent hemoglobin content, 5.5 of the 18 volumes of oxygen is utilized by the tissues. If only 5.5 volumes of oxygen should be available (corresponding to a hemoglobin of 30 per cent), there being no reserve, the oxygen pressure would fall to zero (which occurs only in death) unless some compensatory mechanism intervened. In this event, the patient would be incapable of muscular effort. In carbon monoxide poisoning coma or death follows when only 30 per cent of free hemoglobin remains, the gas being harmful only so far as it prevents oxygenation by combining with the hemoglobin.

Considering the chronicity of pernicious anemia, some mechanism of compensating for the deficit of hemoglobin and the resultant decrease in oxygenation must exist. The increased cardiac output represents this compensatory mechanism. The

1. (*a*) Plesch, J.: Hämodynamische Studien, Ztschr. f. exper. Path. u. Therap. **6**:380, 1909. (*b*) Dautrebande, L.: Le débit cardiaque dans l'anémie, Compt. rend. Soc. de biol. **93**: 1029, 1925. (*c*) Fahr, G., and Ronzone, E.: Circulatory Compensation for Deficient Oxygen Carrying Capacity of the Blood in Severe Anemias, Arch. Int. Med. **29**:331 (March) 1922.

2. (*a*) Bouchut, L., and Froment, R.: Les gros coeurs par anoxémie, Arch. d. mal. du cœur **27**:325, 1934. (*b*) Pickering, G. W., and Wayne, E. J.: Observations on Angina Pectoris and Intermittent Claudication in Anemia, Clin. Sc. **1**:305, 1934. (*c*) Zimmermann, O.: Angina pectoris bei schweren Anämien, Klin. Wchnschr. **14**:847 and 922, 1935. (*d*) Bloch, C.: Herzbeschwerden und Elektrokardiogrammbefunde bei Anaemie, Acta med. Scandinav. **93**: 543, 1938.

3. (*a*) Liljestrand, G., and Stenström, N.: Clinical Studies on the Work of the Heart During Rest: II. The Influence of Variations in the Hemoglobin Content on the Blood Flow, Acta med. Scandinav. **63**:130, 1926. (*b*) Richards, D. W., Jr., and Strauss, M. L.: Circulatory Adjustment in Anemia, J. Clin. Investigation **5**:161, 1928. (*c*) Stewart, H. J.; Crane, N. F., and Deitrick, J. E.: Studies of the Circulation in Pernicious Anemia, ibid. **16**:431, 1937. (*d*) Dautrebande.[1b]

fewer erythrocytes, by moving with increased velocity, make their oxygen-carrying capacity more frequently available. This mechanism is essential for the satisfactory oxygenation of tissue in the presence of a definitely lowered hemoglobin content of the blood.[3c] It leads to changes in the heart.

Cardiac hypertrophy, frequent and marked, has often resulted from anemia produced by hemolysis.[2a] Cardiac enlargement in anemia, without other etiologic basis, has been repeatedly observed.[4] The largest heart weighed 710 Gm.[5] The hypertrophy usually involves the two ventricles equally, the heart being symmetrically enlarged.[2a] Such compensation may be transitory. If the blood improves, the heart returns to normal. With a severe, prolonged anemia the deficit becomes chronic and the hypertrophy persists. Decreased oxygenation of the myocardium may then become a factor in provoking failure of the enlarged heart. Absence of cardiac hypertrophy in an anemia of moderate degree is best explained by the fact that the cardiac output is not appreciably augmented until the hemoglobin falls below 50 per cent, the organism functioning satisfactorily so long as the quantity of hemoglobin is not reduced more than one half.

At low hemoglobin levels the stroke volume, the minute volume output, the cardiac rate and the oxygen consumption are increased. The arm to tongue circulation time is decreased. With a rise in the hemoglobin content of the blood, these changes are reversed. A rise of systolic and diastolic blood pressure also occurs. In spite of the fact that the shortened circulation time, increased cardiac output, decreased hemoglobin and increased oxygen consumption are so related that an organ already working at an accelerated rate is put to the added disadvantage of maintaining a circulation sufficient for the requirements of an increased basal metabolic rate, some believe: (1) that left ventricular work, per beat and per minute, is not increased in anemia; (2) that the work per beat is actually less than when the hemoglobin concentration is normal; (3) that the heart in anemia, at rest and without congestive failure, mechanically performs, commensurately with its size, the work to be expected of it.[3c] It appears that the enlarged heart of anemia is due to anoxemia rather than to increased cardiac work.

Strümpell,[6] in 1886, recognized palpitation as one of the first symptoms of severe anemia; that breathing was hurried due to a feeling of air hunger and shortness of breath and that a feeling of oppression in the breast was characteristic. The prolonged delay in the recognition of the occurrence of angina in anemia seems surprising.[7] Herrick's[8] discussion of 150,[9] 111,[10] 75,[11] 628,[12] 127,[13] 127,[14] 148,[15] 117[16] and 20[17] cases of pernicious anemia recently reported in which the authors made no mention of angina is interesting.

4. (*a*) Goldstein, B., and Boas, E. P.: Functional Diastolic Murmurs and Cardiac Enlargement in Severe Anemias, Arch. Int. Med. **39**:226 (Feb.) 1927. (*b*) Ball, D.: Change in the Size of the Heart in Severe Anemia with Report of a Case, Am. Heart J. **6**:517, 1931. (*c*) Ellis, L. B.: The Effect of Severe Anemia on the Heart and Circulation, J. Clin. Investigation **14**:715, 1935.

5. Cabot, R. C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926.

6. von Strümpell, A.: Lehrbuch der speziellen Pathologie und Therapie der inneren Krankheiten für Studierende und Aerzte, eds. 23 and 24, Leipzig, F. C. W. Vogel, 1922, vol. 2.

7. Herrick, J. B., and Nuzum, F. R.: Angina Pectoris: Clinical Experience with Two Hundred Cases, J. A. M. A. **70**:67 (Jan. 12) 1918.

8. Herrick, J. B.: On the Combination of Angina Pectoris and Severe Anemia, Am. Heart J. **2**:351, 1927.

9. Levine, S. A., and Ladd, W. S.: Pernicious Anemia: A Clinical Study of One Hundred and Fifty Consecutive Cases with Special Reference to Gastric Anacidity, Bull. Johns Hopkins Hosp. **32**:254, 1921.

Long ago Herrick said that "blood of poor quality going through somewhat narrowed coronary arteries, might favor, on slight provocation, the development of an anginal attack."[7] The occurrence of angina in anemia[7] has been repeatedly confirmed.[18] The relative infrequency of this syndrome has, likewise, been confirmed.[19] Comparatively few patients with angina are found in the many large series of cases of pernicious anemia investigated.[20] Many single case reports appear in the literature.[21]

The anemic patient may experience dyspnea, dizziness, angina or claudication.[2b] With sclerosis of the coronary or limb arteries, activity may provoke angina or claudication. Without these symptoms, dyspnea or dizziness may develop. Dyspnea or dizziness may so limit the patient's activity as to prevent the occurrence

10. Willson, C. R., and Evans, F. A.: An Analysis of the Clinical Histories of Patients with Pernicious Anemia in the Johns Hopkins Hospital from 1918-1922 inclusive, Bull. Johns Hopkins Hosp. **35**:38, 1924.

11. Campbell, J. M. H., and Conybeare, J. J.: Addison's Anaemia: A Study of Seventy-Five Cases, with Some Remarks on the Pathology, Guy's Hosp. Rep. **72**:265, 1922.

12. Giffin, H. Z., and Bowler, J. P.: Diseases Which May Be Associated with Pernicious Anemia, Minnesota M. J. **6**:13, 1923.

13. Braun, L.: Ueber Angina pectoris, Wien. klin. Wchnschr. **39**:265 and 305, 1926.

14. Rohner, F. J.: Pernicious Anemia: A Study of One Hundred and Twenty-Seven Cases, Iowa State M. Soc. **12**:216, 1922.

15. Carr, J. G.: Pernicious Anemia: A Study of One Hundred and Forty-Eight Cases, Am. J. M. Sc. **160**:737, 1920.

16. Panton, P. N.; Maitland-Jones, A. G., and Riddoch, G.: Pernicious Anemia: An Analysis of One Hundred and Seventeen Cases, Lancet **1**:274, 1923.

17. Reid, W. D.: The Heart in Pernicious Anemia, J. A. M. A. **80**:534 (Feb. 24) 1923.

18. (*a*) Coombs, C. F.: A Note on the Cardiac Symptoms of Pernicious Anemia, with Particular Reference to Cardiac Pain, Brit. M. J. **2**:185, 1926. (*b*) Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, Arch. Int. Med. **41**:769 (June) 1928. (*c*) Reichel, J.: Beiträge zur Kenntnis der perniziösen Anämie und der akuten Leukämien, Wien. Arch. f. inn. Med. **19**:241, 1929; abstracted, J. A. M. A. **94**:756 (March 8) 1930. (*d*) Porter, W. B.: The Association of Angina Pectoris and Anemia, Virginia M. Monthly **58**:806, 1932. (*e*) Wilkinson, J. F.: Diseases Associated with Pernicious Anemia: Study of Three Hundred and Seventy Cases, Quart. J. Med. **6**:281, 1933. (*f*) Hochrein, M., and Matthes, K.: Anämie und Angina pectoris, Deutsches Arch. f. klin. Med. **177**:1, 1934. (*g*) Paschkis, K.: Anämie und Angina pectoris, Klin. Wchnschr. **13**: 767, 1934. (*h*) Bloch, C.: Angina pectoris und Anämie, Wien. Arch. f. inn. Med. **26**:143, 1934; (*i*) footnote *2 d*. (*j*) Hunter, W.: The Nervous and Mental Disorders of Severe Anemias in Relation to Their Infective Lesions and Blood Changes, Proc. Roy. Soc. Med. **16**:1, 1922. (*k*) Sturgis, C. C.: Angina Pectoris as a Complication in Myxedema and Exophthalmic Goiter, Boston M. & S. J. **195**:351, 1926. (*l*) Conner, L. A., in discussion on Herrick, J. B.: Combination of Angina Pectoris and Severe Anemia, Tr. A. Am. Physicians **42**:23, 1927. (*m*) Levine, S. A., in discussion on Herrick, J. B.: Combination of Angina Pectoris and Severe Anemia, ibid. **42**:23, 1927. (*n*) Carey, J. B.: Pernicious Anemia with Fatal Termination During a Liver Diet: Report of Three Cases, Arch. Int. Med. **47**:893 (June) 1931. (*o*) Witts, L. J.: Chronic Microcytic Anemia, Brit. M. J. **2**:883, 1931. (*p*) Gwyn, N. B.: On the Angina Pectoris Occurring in the Course of Certain Anemias, Canad. M. A. J. **26**:26, 1932. (*q*) Elliott, A. H.: Anemia as the Cause of Angina Pectoris in the Presence of Healthy Coronary Arteries and Aorta: Report of Case, Am. J. M. Sc. **187**:185, 1934. (*r*) Beach, C. H.: Anginal Symptoms Associated with Certain Constitutional Diseases, J. A. M. A. **105**:871 (Sept. 14) 1935. (*s*) Stalker, H.: Angina Pectoris and Pernicious Anemia: A Résumé of the Literature, with a Case Report, Ann. Int. Med. **10**:1172, 1937. (*t*) Vatcher, S.: Angina in Pernicious Anemia, with Electrocardiographic Changes and Abdominal Aneurysm, Lancet **2**:192, 1939. (*u*) Bouchut and Froment.[2a] (*v*) Pickering and Wayne.[2b] (*w*) Zimmermann.[2c] (*x*) Herrick.[8]

19. Herrick.[8] Hochrein and Matthes.[18f]

20. Bouchut and Froment.[2a] Pickering and Wayne.[2b] Zimmermann.[2c] Coombs.[18a] Keefer and Resnick.[18b] Reichel.[18c] Porter.[18d] Wilkinson.[18e] Hochrein and Matthes.[18f] Paschkis.[18g] Bloch.[18h] Bloch.[2d]

21. Hunter.[18j] Sturgis.[18k] Conner.[18l] Levine.[18m] Carey.[18n] Witts.[18o] Gwyn.[18p] Elliott.[18q] Beach.[18r] Stalker.[18s] Vatcher.[18t]

of angina or claudication. In other patients, these symptoms being less readily induced, exercise results in angina or claudication, even in the absence of local vascular disease.

The hypothesis of relative myocardial ischemia as the cause of pain in angina, considered by Jenner,[22] Parry [23] and later by Allan Burns [24] and MacKenzie,[25] has been revived.[18b] Recent evidence [26] indicates that the pain of angina and claudication are due to a similar mechanism; a stimulation of nerve endings in the tissue spaces of the active muscles by a chemical or physicochemical change, factor P, representing the accumulation of products formed during muscular contraction and ordinarily removed by oxidation. The increased circulation rate (decreased circulation time) generally accepted as occurring in anemia [3] is not accompanied by an increased flow through the limbs.[27] In fact, during contraction, the blood flow through a muscle is reduced, owing to compression of blood vessels.[28] A great increase in blood flow occurs soon after contraction, thereby providing a supply of oxyhemoglobin adequate to remove "factor P" very quickly, even in the anemic state.[2b] Claudication in anemia has been observed.[29] In a series of 25 cases of severe anemia, 6 of the 7 patients with claudication were free from attacks after control of their anemia.[2b] Claudication occurred once in our series and was relieved by control of the anemia. Cardiac hypertrophy may be a factor in the production of myocardial ischemia. Anemia predisposes to coronary inadequacy during exertion.[30]

A change in the heart rate occurs in anemia.[2] The pain of angina has been closely related to a rise in cardiac rate with its associated increased energy expenditure of the heart.[26c] This rise in pulse rate after exercise is greater in the anemic than in the nonanemic state.[2b] Changes in blood pressure occur in anemia, the pressure, before and after exercise, often being reduced.[31] The coronary circulation is decreased considerably by such a fall in the mean arterial pressure.[32]

The decrease in the supply of oxygen explains the coronary insufficiency occurring in anemia and in carbon monoxide poisoning.[33] Angina in methemo-

22. Jenner, E., cited by Fulton, F. T.: Coronary Artery Disease: A Historical Sketch, Ann. Int. Med. **11**:1433, 1938.

23. Parry, C. H.: Inquiry into the Symptoms and Causes of the Syncopa Anginosa, Commonly Called Angina Pectoris, London, Cadell & Davies, 1799.

24. Burns, A.: Observation of Some of the Most Frequent and Important Diseases of the Heart, Edinburgh, James Muirhead, 1809.

25. MacKenzie, J.: Diseases of the Heart, London, Oxford University Press, 1908.

26. (*a*) Lewis, T.; Pickering, G. W., and Rothschild, P.: Observations upon Muscular Pain in Intermittent Claudication, Heart **15**:359, 1931. (*b*) Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, Am. Heart J. **8**:729, 1933. (*c*) Wayne, E. J., and LaPlace, L. B.: Observations on Angina of Effort, Clin. Sc. **1**:103, 1934. (*d*) Kissin, M.: The Production of Pain in Exercising Skeletal Muscle During Induced Anoxemia, J. Clin. Investigation **13**:37, 1934. Pickering and Wayne.[2b]

27. Hewlett, A. W., and Van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm, Heart **1**:87, 1910. Stewart, G. N.: Studies on the Circulation in Man: VI. Observations on the Blood Flow in the Hands (Mainly) in Cases of Anemia, J. Exper. Med. **18**:113, 1913.

28. Anrep, G. V.; Blalock, A., and Samaan, A.: The Effect of Muscular Contraction upon the Blood Flow in the Skeletal Muscle, Proc. Roy. Soc., London, s.B **114**:223, 1934.

29. Pickering.[2b] Bloch.[18b] MacKenzie.[25]

30. Fahr, G. E.: Hypertension Heart: The Most Common Form of So-Called Chronic Myocarditis, J. A. M. A. **80**:981 (April 7) 1923. Elliott.[18q]

31. Pickering.[2b] Wayne.[26c]

32. Anrep, G. V., and King, B.: The Significance of the Diastolic and Systolic Blood Pressures for the Maintenance of the Coronary Circulation, J. Physiol. **64**:341, 1928.

33. Gotsch, K.: Therapie der Myokardschäden, Med. Klin. **32**:275, 1936.

globinemia, from benzene poisoning, diagnosed as heart disease has been reported.[34] That a severe anemia may inaugurate an angina, particularly in the presence of an existing organic disturbance of the coronary circulation, is recognized. Angina may occur in any kind of organic heart disease coincidentally with anemic fluctuations. The improvement or complete cessation of angina following transfusion,[35] or anti-anemic therapy,[36] has been recorded. In a woman with primary and in one with secondary anemia, angina was so severe that they sought treatment for that reason only.[2e] The angina was relieved with control of the disease of the blood. Five cases of angina in anemia with normal coronary arteries have been described.[37] In most instances angina occurs only when there is some associated coronary disease. By lowering the oxygen supply to the heart still further, the anemia reveals, clinically, a permanent limitation of coronary blood flow unsuspected under ordinary circumstances.[2b] Many doubt that anemia will initiate an attack of angina without some background of coronary disease, insisting that marked anoxemia does not produce angina if the coronary arteries are functionally and organically sound.[38] Angina in youth is rare.[18f]

Some believe that an increased vagal tonus alone may cause disturbance in the coronary circulation and that this vagotonia, as well as coronary disease, may initiate angina. In coronary sclerosis a rise in tonus may be due to vasomotor factors.[39] The results of lumbar sympathectomy for claudication support this view. Thus the cardiovascular manifestations may not be due entirely to anemia with its resultant myocardial anoxemia.[40] Cardiac complaints, including angina, may be entirely absent in a form of heart disease predisposed to angina, even in the presence of a severe anemia with necropsy evidence of marked myocardial change due to the anemia.[18h] A man of 64 years with a hemoglobin reading of 30 per cent never experienced angina, in spite of extensive coronary sclerosis found at necropsy. A full, energetic and prolonged life may be enjoyed in spite of severe anemia.[18f]

Reports of 5.5 per cent of 3,400 patients observed over a period of 20 years [41] and 3.45 per cent of 4,000 who came to autopsy [5] probably express the true percentage incidence of angina in older people. Disagreement exists as to the frequency of occurrence of angina in anemia. Reports of 8 instances in 25 cases,[2b] 8 in 36,[18a] 3 in 370,[18e] 13 in 140 [18h] and 43 in 1,560 [35] are representative of the variation in the reported incidence of angina in anemia. In a report of 113 cases of primary and 327 of secondary anemia, along with 297 cases of angina pectoris, the instances of anemia comprised 1.7 per cent of the cases of angina pectoris.[18f]

Severe anemia does not occur often in youth. Usually it is due to sudden loss of blood from injury or abortion which confines the patient to bed, the effects of exertion being avoided.[2d] Pernicious anemia occurs later in life. In 500 cases

34. Schilling, V.: Die Wechselbeziehungen von Atmung und Kreislauf, Leipzig, Theodor Steinkopff, 1935.

35. Willius, F. A., and Giffin, H. Z.: The Anginal Syndrome in Pernicious Anemia, Am. J. M. Sc. **174**:30, 1927. Levine.[18m]

36. Pickering.[2b] Zimmermann.[2c] Bloch.[2d] Bloch.[18h]

37. Cabot.[5] Elliott.[18q] Willius.[35]

38. von Bergmann, G.: Funktionelle Therapie, ed. 2, Berlin, Julius Springer, 1936. Zimmermann.[2c] Levine.[18m] Stalker.[18s]

39. Romberg, E.: Ueber Koronarsklerose, München. med. Wchnschr. **79**:1021 and 1065, 1932.

40. Szerkely, P.: Electrocardiographic Findings in Anemia, Brit. Heart J. **2**:1, 1940. Goldhammer, S., and Scherf, D.: Elektrokardiographische Untersuchungen bei Kranken mit Angina pectoris, Ztschr. f. klin. Med. **122**:134, 1932.

41. Edens, E.: Die Krankheiten des Herzens und der Gefässe, Berlin, Julius Springer, 1929.

of angina due to uncomplicated arteriosclerosis the average age of the patients was 65,[42] whereas in series of cases of angina associated with anemia the average ages were from 42.3 [2d] to 53.5 [35] years. Among persons with the angina of organic heart disease there is a predominance of males, only 25 per cent of 500 patients being females.[42] This is not true of the angina of anemia. Of 250 patients, 85 with primary and 165 with secondary anemia, 82 were males and 168 females, and of the 18 having angina, 5 were men and 13 women.[2c] Of 43 patients with angina among 1,560 anemic patients, 27 were males and 16 were females.[35] Of our 300 patients with pernicious anemia, 163 were males and 137 females. No direct relationship exists between the severity of the anemia and the appearance of angina.[35] Although angina usually occurs with hemoglobin levels of 30 to 40 per cent, nevertheless, in a group of 250 cases 27 of the patients with the most severe anemia (20 having a Sahli reading under 20 per cent and 22 with an erythrocyte count below 1,000,000) had no angina.[2c] The mortality of anemic patients with angina is low; 1 in 13,[18h] 1 in 43,[35] 2 in 4 primary and 2 in 12 secondary anemias.[2c] Contrasting sharply with this, 213 of 500 patients with angina of uncomplicated heart disease died within 4.4 years.[42]

There is a great possibility of error in attempting to segregate patients with anemia having cardiovascular involvement.[2d] Low mortality and lack of necropsies interfere with the ready exclusion of organic cardiovascular disease in patients with pernicious anemia who have angina. Statistical studies are undependable. Angina is frequently not recorded or not inquired about by the examiner.

Other cardiovascular complaints are more common than angina and claudication.[43] They are not restricted to any type of anemia and are not related to the severity of the anemia.[40] With dyspnea, an enlarged heart and murmurs, the disease frequently gives the appearance of heart disease. In 10 of 36 cases of anemia, the initial diagnosis was heart disease; 6 patients were elderly persons with angina or dyspnea and edema.[18a] Other instances of anemia, mistaken for primary heart disease, have been reported.[44]

In this study an outspoken relationship was noted between cardiovascular complaints and the disease of the blood. With improvement in the condition of the blood the cardiovascular manifestations lessened. Anemia may bring out cardiac symptoms in a patient with involvement of the heart. In 4 of the 6 patients with mitral stenosis, symptoms first developed with the onset of anemia. With improvement of the blood picture, 2 of these were relieved. In the present series, the occurrence of cardiovascular symptoms and findings with hematologic decompensation and their disappearance following treatment or during a remission are striking. Since angina or any other cardiovascular symptom may be the initial or outstanding evidence of severe disease of the blood,[45] these manifestations, even when accompanied by such graphic changes as low voltage, displacement of the ST interval or even definite flattening of the T wave, do not necessarily mean primary heart disease. All these signs, the usual criteria of primary cardiovascular disease, may occur solely as the result of severe anemia. Hematologic examination is the only dependable means of differentiation. It is important in angina to rule out anemia as a determining or contributing factor, especially if the angina is

42. White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of Five Hundred Cases of the Former Condition and of Two Hundred of the Latter, Am. Heart J. **7**:1, 1931.

43. Ellis.[4c] Hochrein and Matthes.[18f]

44. Jagic, N., and Klima, R.: Klinik und Therapie der Blutkrankheiten, ed. 2, Berlin, Urban & Schwarzenberg, 1934. Schilling.[34] Von Bergmann.[38]

45. Coombs.[18a] Bloch.[18b]

associated with palpitation, dyspnea, enlarged heart, systolic murmur, low arterial pressure, edema or urobilinogenuria. If anemia is present, a therapeutic test may be necessary to determine its role in the production of cardiac symptoms.

With acute anoxemia a known cause of such a variety of changes in the electrocardiogram, it is surprising that so few graphic changes have been reported in severe anemia. With "tiger heart" commonly resulting from long-standing anemia and with the anemic heart behaving clinically as though myocarditis were present, this lack of graphic evidence is surprising.[46] In 20,[17] 113,[18f] 12 [85] and 15 [47] cases of pernicious anemia significant graphic changes were not recorded.

Conduction defects resulting from anemia have long been recognized.[48] In 2 of 10 patients severely ill with anemia, the PR interval was abnormally prolonged.. It returned to within normal limits after correction of the anemia (from 0.265 second duration with hemoglobin of 33 per cent to 0.19 second with hemoglobin of 97 per cent and from 0.205 second duration with hemoglobin of 38 per cent to 0.145 second with hemoglobin of 110 per cent).[2b] Other graphic changes in anemia have been reported.[49] Displacement of the ST interval simulating that

TABLE 1.—*Distribution of Patients According to Age and to Presence of Cardiovascular Manifestations*

Age, Yr.	Without Cardiovascular Manifestations	With Cardiovascular Manifestations	Total
20-24	0	1	1
25-29	1	5	6
30-34	2	11	13
35-39	4	14	18
40-44	1	20	21
45-49	9	27	36
50-54	9	34	43
55-59	9	46	55
60-64	6	40	46
65-69	2	33	35
70-74	0	21	21
75-79	0	4	4
80-84	0	1	1
Total	43	257	300

of coronary occlusion has been described.[50] Many have described T waves of low amplitude,[51] displacement of the ST interval,[52] and low voltage [51] in anemia, with [18f] and without [53] apparent heart disease.

PERSONAL OBSERVATIONS

Inconsistencies in the reported incidence of angina in anemia led us to determine its incidence in a large series of patients. The other symptoms and findings

46. Hochrein and Matthes.[18f] Bloch.[2d]

47. Smith, K. S.: The Nutrition of the Heart in Relation to the Electrocardiogram and Anginal Pain, Lancet **1**:632, 1933.

48. Lewis, T., and Mathison, G. C.: Auriculo-Ventricular Heart-Block as a Result of Asphyxia, Heart **2**:47, 1910. Mathison, G. C.: The Cause of the Heart-Block Occurring During Asphyxia, Heart **2**:54, 1910.

49. Zimmermann.[2c] Hochrein and Matthes.[18f]

50. (*a*) Dietrich, S., and Schwiegk, H.: Das Schmerzproblem der Angina pectoris, Klin. Wchnschr. **12**:135, 1933. (*b*) Kountz, W. B., and Hammouda, M.: Effect of Asphyxia and of Anoxemia on the Electrocardiogram, Am. Heart J. **8**:259, 1933. (*c*) Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, ibid. **8**:745, 1933. Paschkis.[18g]

51. Bloch.[2d] Bloch.[18b]

52. Bloch.[2d] Bloch.[18b] Elliott.[18q] Dietrich.[50a] Kountz.[50b] Rothschild.[50c]

53. Bloch.[2d] Bloch.[18b] Elliott.[18q]

(dyspnea, cardiac enlargement and edema) so overshadowed our original interest that they demanded major consideration.

We reviewed the histories of 300 authenticated cases of pernicious anemia from the standpoint of cardiovascular symptoms and findings (table 1). There were 257 with and 43 without cardiovascular manifestations. There were 298 white (99 per cent) and 2 Negro (1 per cent) patients; 163 men (54 per cent) and 137 women (46 per cent). Seventy-four (25 per cent) of the patients died, and necropsy was performed on 6 (2 per cent). No attempt was made to segregate those having primary cardiac disease when the patients were classified according to the presence of cardiovascular manifestations. The incidence of various symptoms and findings in our 300 patients is shown in table 2. Of the 79

TABLE 2.—*Symptoms and Findings of Organic Heart Disease*

	Number of Cases	Per Cent		Number of Cases	Per Cent
Angina	3	1	Basal rales	21	7
Precordial pain (nonanginal)	38	12	Edge of liver down	79	26
Weakness	231	77	Liver tenderness	9	3
Dyspnea	154	51	Apical systolic murmur	144	48
Palpitation and tachycardia	66	22	Apical presystolic murmur	5*	1
Dizziness	26	8	Apical diastolic murmur	7	2
Scotomas	13	4	Basal systolic murmur	58	17
Tinnitus	3	1	Basal diastolic murmur	7	2
Displacement of left cardiac border	87	29	Aortic systolic murmur	31	10
Edema of ankles	104	34	Transmitted murmur	11	3

* Two of these patients had a presystolic thrill in addition to the murmur.

patients showing enlargement of the liver, the edge was below the costal margin 1 cm. in 24, 2 cm. in 17, 3 cm. in 14, 4 cm. in 10 and 5 cm. in 5; the distance was not recorded for 9 patients. In 54 of the 300 cases the blood pressure was not recorded. In the other 246 cases the readings were as follows:

Pressure	No. of Cases
<100/60	49
<120/80	96
<140/90	60
>140/90	41

The duration of symptoms in 259 cases was as follows (in 41 cases there was no record):

Duration of Symptoms	No. of Cases
1- 3 mo.	53
3- 6 mo.	26
6-12 mo.	31
1- 2 yr.	56
2- 3 yr.	30
3- 4 yr.	22
4- 5 yr.	11
5- 6 yr.	18
7 yr.	3
8 yr.	1
9 yr.	1
10 yr.	4
14 yr.	1
15 yr.	2

The erythrocyte counts were:

No. of Red Cells	No. of Cases
Less than 500,000	3
500,000-1,000,000	90
1,000,000-2,000,000	119
2,000,000-3,000,000	46
3,000,000-4,000,000	16
4,000,000-5,000,000	6
More than 5,000,000	4

No count was recorded on the current chart in 16 cases. These, along with the last 4 cases, were instances of readmission of patients with pernicious anemia. In 212 of the 300 cases the erythrocyte count was below 2,000,000.

The leukocyte counts of 280 patients were normal or decreased proportionately to the decrease in hemoglobin and red cells except in 3 instances. A woman aged 45 with a leukocyte count of 20,400 died of bronchopneumonia on her eighth day in the hospital. A woman aged 70 with cardiac decompensation and an infection of the upper respiratory tract had a leukocyte count of 16,700 just before death. Another woman, aged 76, with organic heart disease and a blood pressure of 194 systolic and 100 diastolic had an unexplained rise of leukocytes to 13,600.

CASE HISTORIES

CASE 1.—A man 44 years old, ill nine months with dyspnea, palpitation, edema of the ankles, enlargement of the heart, an apical systolic murmur, the edge of the liver 1 cm. below the costal margin and the blood pressure 140 systolic and 70 diastolic, had been unsuccessfully treated for organic heart disease with decompensation for two months. He had gained 40 pounds (18 Kg.). Pernicious anemia was discovered (hemoglobin content 35 per cent, erythrocyte count 1,340,000, color index 1.4 and leukocyte count 3,800). Treatment of cardiovascular decompensation with proper control of the anemia gave prompt relief. The weight returned to normal.

CASE 2.—A man of 35 years, unable to walk because of changes in the spinal cord, with precordial pain, dyspnea, palpitation, apical and basal systolic murmurs and the edge of the liver 1 cm. below the costal margin, had a hemoglobin content of 30 per cent, an erythrocyte count of 1,330,000, a color index of 1.1 and a leukocyte count of 6,700. All abnormalities except the murmurs definitely improved with management of the anemia alone. The patient left the hospital six months later.

CASE 3.—A man aged 47, ill seven months and treated for heart disease, was admitted to the hospital in coma. His hemoglobin content was 20 per cent, the erythrocyte count 770,000, the color index 1.3 and the leukocyte count 3,100. There were dyspnea, edema of the ankles and an apical systolic murmur. The left cardiac border was 3 cm. outside the midclavicular line; the edge of the liver was 8 cm. below the ribs, and the spleen was felt 2 cm. below the umbilicus. Response to injections of liver extract was satisfactory. All symptoms and findings cleared promptly. The patient was discharged on the fifty-seventh day of hospitalization as having made "a remarkable recovery."

CASE 4.—A man aged 59, ill two years, admitted to the hospital in a second relapse, with a hemoglobin content of 20 per cent, an erythrocyte count of 740,000, a color index of 1.3 and a leukocyte count of 2,540, complained of dyspnea, edema of the ankles and precordial pain of six months' duration. Control of the anemia relieved all symptoms.

CASE 5.—A man aged 58, with a hemoglobin content of 40 per cent, an erythrocyte count of 1,400,000, a color index of 1.43 and a leukocyte count of 3,700, had anginal pain, dyspnea, edema of the ankles, definite enlargement of the heart, apical and aortic systolic murmurs with fibrillation and a history of rheumatism twenty years previously. He was relieved by treatment of the anemia.

CASE 6.—A man aged 43, with a hemoglobin content of 30 per cent, an erythrocyte count of 1,260,000, a color index of 1.15 and a leukocyte count of 3,400, had dyspnea, pain in the right side of the chest, edema of the ankles, enlargement of the left side of the heart, an apical presystolic murmur and thrill and an aortic diastolic murmur. He was relieved by management of the anemia.

CASE 7.—A man aged 52, ill six months with cardiac failure and definite hematologic decompensation, whose condition appeared terminal on his admission to the hospital, was comfortable after four days of liver therapy. A PR interval of 0.34 second decreased to 0.19 second.

CASE 8.—A man aged 61 with mild cardiac and hematologic failure of five years' duration had moderately severe cramps in the muscles of his calves, which disappeared with control of the anemia.

SUMMARY

Cardiovascular manifestations were found in 257 of 300 cases of pernicious anemia. In the presence of severe anemia it is impossible to segregate dependably patients with primary cardiovascular involvement. All of the usual criteria of cardiovascular disease may occur solely as the result of anemia. These symptoms and findings are not restricted to any type of anemia or related to the severity of the anemia. Examination of the blood is essential for dependable differentiation. Cardiovascular manifestations often occur with hematologic decompensation and disappear after treatment or during a remission.

HYPERTENSION IN ONLY ONE OF IDENTICAL TWINS

REPORT OF A CASE, WITH CONSIDERATION OF PSYCHOSOMATIC FACTORS

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Because it has been assumed rather generally that the heredity patterns of identical twins are essentially similar, a study of any disease process affecting identical twins is of importance in that it may suggest the presence or absence of heredity factors in the pathogenesis of this particular disease. A study of cardiovascular disease occurring in identical twins may have such pertinence.

Electrocardiographic studies [1] of identical twins have shown that, although the electrocardiograms of identical twins are similar in many instances, they are not always so and may be considerably different.

Rheumatic fever with carditis in each of a pair of identical twins has been reported by Morgan and Webster [2] and by Perry.[3] However, the latter author also reported the occurrence of rheumatic fever in but one of another pair of identical twins and concluded that, while heredity may be of considerable importance in the pathogenesis of rheumatic fever, infection plays an equally important role. In all of these reported cases of rheumatic fever the environments of the twins were also identical. This fact obscures the actual role played by the hereditary factors.

Congenital cardiac defects [4] have also been reported in each of identical twins. Kahler and Weber [5] further observed that the frequency of such defects in identical twins was twice that found in nonidentical twins.

Parade and Lehmann [6] reported the occurrence of angina pectoris in identical twins. These twins died within a year of each other; both had a thrombosis of the descending branch of the left coronary artery and a myocardial infarct in the same region of the heart. The environments of these two men were not similar.

Essential hypertension also has been reported [7] in identical twins with similar environment.

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From the Harold Brunn Institute for Cardiovascular Research and the Department of Psychiatry, Mount Zion Hospital.

1. Wise, H. B.; Comeau, W. J., and White, P. D.: An Electrocardiographic Study of Twins, Am. Heart J. **17**:201, 1939.

2. Morgan, J. E., and Webster, S. J.: Rheumatic Fever Followed by Mitral Heart Disease in Each of Identical Twins, J. A. M. A. **110**:1744 (May 21) 1938.

3. Perry, C. B.: Rheumatic Heart Disease in Identical Twins, Arch. Dis. Childhood **15**:177 (Sept.) 1940.

4. Giustra, F. X., and Tosti, V. G.: True Cor Biloculare in Identical Twins, Am. Heart J. **17**:249, 1939.

5. Kahler, O. H., and Weber, R.: Zur Erbpathologie von Herz- und Kreislauferkrankungen, Ztschr. f. klin. Med. **137**:507, 1940.

6. Parade, G. W., and Lehmann, W.: Angina pectoris bei erbgleichen Zwillingen, Klin. Wchnschr. **17**:1036, 1938.

7. Fröhlich, K.: Jugenliche Zwillinge mit arteriellen Hochdruck, Med. Klin. **33**:1196, 1937.

In the present communication we are reporting the results of a study of identical twins in only one of whom hypertension and coronary disease were present. Each twin was subjected to a routine physical examination, a psychologic assay, an electrocardiographic study and determination of the renal blood flow and of the glomerular filtration rate.

UNIOVULAR ORIGIN OF THE TWINS HEREIN REPORTED ON

Although the only incontrovertible proof of the uniovular origin of twins is the finding of a single placenta at the time of their delivery, Newman [8] listed other criteria which in his opinion establish the identity of twins. The birth records of our twins are not available, since the physician who delivered them is dead and the records were lost. We thus do not know if there was one placenta. Newman's criteria were met by our set of twins, for they had (*a*) identical color, texture and form of hair, (*b*) striking similarity in general appearance (fig. 1), (*c*) identical color and color pattern of the iris, (*d*) identical color and texture of skin, (*e*) identical eyelashes, eyebrows, lips, shape of ears and teeth, (*f*) identical hands, fingers and finger nails, (*g*) identical general character patterns and main lines of finger and palm prints, and (*h*) blood of the same type.

The evidence of blood type is of especial importance in these twins. A serologic study was done by Dr. Charles Weiss, director of clinical laboratories, Mount Zion Hospital, San Francisco, and Dr. Phillip Levine, bacteriologist of Beth Israel Hospital, Newark, N. J., who have done special work in this field. The blood of both the twins was of the following type: A, M+, N+, Rh—, Hr+. Such an agreement in blood type is an almost incontrovertible proof of the identity of the twins. Although such similarity in the blood of two persons is possible statistically, practically it is impossible to find it unless they are identical twins. One must remember that even identical twins show a certain amount of variation. This was true in our twins: The healthy twin was always more robust physically, and when both grew up the healthy twin weighed 30 to 50 pounds (13 to 23 Kg.) more than the patient. Intellectually, the healthy twin was also more alert and was slightly ahead of the patient in school.

CASE STUDY OF THE PATIENT AND OF HIS BROTHER

Clinical Study.—The patient, G. G., was a man aged 54 at the time we saw him. In 1931 he was found to have hypertension. However, at this time he experienced no symptoms. In 1937 a routine electrocardiogram was taken, apparently because of his persisting hypertension. It was not until 1939, however, that he began to have attacks of severe substernal pain radiating down his left arm. These attacks were particularly likely to occur after strenuous exertion, excitement or ingestion of a heavy meal. Usually they subsided within several minutes if nitroglycerin was given. The frequency and severity of his attacks increased until he was forced to quit work at the end of 1940. When seen by us in February 1941, he had daily attacks of anginal pain. There was no familial history of hypertension. The patient had never been exposed to toxic quantities of lead and had never used tobacco in any form. He had lived in San Francisco from birth.

On physical examination the patient was observed to be a robust, vigorous person, in no obvious distress or pain. Examination of his eyes revealed a moderate tortuosity of his retinal arteries, with marked auriculoventricular depression. No hemorrhagic or exudative areas were seen in the retina of either eye. Examination of the heart revealed no murmurs, but numerous extrasystoles were heard, apparently ventricular in origin. Fluoroscopic examination showed a moderate dilatation of the ascending aorta and slight enlargement of the left ventricle. The radial arteries felt thickened. The blood pressure (right brachial artery) was 180 systolic and 110 diastolic. There were no peripheral signs of cardiac decompensation.

8. Newman, H. H.: Multiple Human Births, New York, Doubleday, Doran & Company, Inc., 1940.

Intravenous pyelography showed no gross abnormality of the kidneys. Microscopic and chemical examination of the urine likewise failed to reveal any abnormality.

R. G., the twin brother of the patient, had never had any signs or symptoms suggestive of cardiovascular disease. He submitted to the diagnostic procedures herein reported because he wished to aid in this study. He also had never used tobacco in any form.

On physical examination the patient was observed to be a calm, apparently healthy person. Examination of his eyes revealed no abnormalities either of the retina or of the retinal vessels. Examination of the heart showed no abnormality in size, rhythm or dynamics. The radial arteries were not palpably thickened. The blood pressure (right brachial artery) was 135 systolic and 80 diastolic.

Microscopic and chemical examination of the urine gave negative results.

Personality Study.—The patient, a large, stocky middle-aged man, aged 54, was eager to have the examination completed as soon as possible so that he could start on his vacation. He was tense, somewhat restless and always in a hurry. He gave a history of his illness along the lines already reported.

The patient came from sturdy Irish-German stock. His mother was living and well at 77 years of age, a tense, nervous woman. The patient's father died at the age of 65, from pernicious anemia.

The patient stated that he was a twin, being thirty-five minutes older than his brother. He described his brother as being somewhat taller than he and always weighing about 50 pounds more than he. As infants they could not be told apart and had to have blue and

Fig. 1.—The twins at the age of 3 years.

pink ribbons to identify them. The brother was a better scholar, but the patient was a better mixer. From early adolescence the patient had joined all kinds of organizations; currently he was a Woodsman, a thirty-fifth degree Scottish Rite Mason, a member of a band and a participant in other activities.

As a child, the patient was very active, and at the age of 11 years he began to work in an engraving shop. At the same time he continued in an evening grammar school. He was able to complete an evening high school course. At the age of 18, the patient entered the United States postal service, where he made a good record. It was his job, finally, to teach the younger postal clerks how to work more efficiently, and he was made a "speed-up man," that is, he was to set the pace for the slower men to follow. The patient made such an excellent record in the postoffice that one of the larger banks employed him to take charge of their mail department. Soon afterward he was put in charge of the young men who were in training at the bank. Irrespective of previous education, the young men who expected to make a career in the bank had to start in the patient's department as messengers and junior clerks. He built crews of men, one after another, from which the stable organization of the bank was supplied. He took responsibility for their later performances.

As to personality, the patient was dynamic, eager, quick, excitable; anything he did, he "jumped" to do. It was this quality that made him known as a "builder of men" and as an example for young men to follow. His wife described him as a man of a worrisome nature; he never let a bill go and everything had to move ahead of schedule. He constantly worried about whether his work was done well and at night thought about his work and went over details again and again. He was very friendly and had no enemies. He continually did favors for other people. The patient described himself as "too damned conscientious" and "too serious." There was a certain strain about him, and he always seemed to be too busy to do

things easily. The patient described himself as being very sensitive, never letting anybody know how he felt, never, never letting himself go and always concealing his emotions. To his wife he was a "high pressure" man who rarely lost his temper. She did not feel that he was very sensitive, but she felt herself to be sensitive, because of crying easily. She stated that he never showed how he really felt and that whatever he wanted to do he did in a hurry, "skipping and jumping" all the time. His wife said, further, that he always slept poorly and got up at 5 a. m., although there was no need for it, and as he got older he seemed to be more and more on the go. Sexually, the patient was described as an "overly passionate man." The patient had one child, a woman of 31 who was married and happy.

The patient's brother, R. G., looked strikingly like the patient. He had the same build and the same facial expression; especially, their voices were strikingly alike. R. G. repeated stories of how alike they were as children and gave numerous incidents of how they were confused. They could not be told apart at school. The patient seemed to R. G. more of a nervous type, whereas R. G. himself was steadier and more easy going. R. G. said G. G. was a restless person who could not sit still. The patient had several changes of jobs, always being more ambitious and eager than the brother.

Similar and Contrasting Characteristics

(In the patients' own words)

Patient	*Brother*
Nickname: "Speed-up George"	Nickname: "Lead-in-the-pants"
Nervous type	Not so nervous
Fast worker	Also fast, but not so fast
Always on the go; flies to things Always "bing-bing"	Excited occasionally, but not so excitable
Played tackle in high school (145 pounds [65 Kg.])	Played center in high school (165 pounds [74 Kg.])
Usual weight, 175 pounds (79 Kg.)	Usual weight, 225-250 pounds (101 to 112 Kg.)
He was the wilder of the two, always feeling more devilish	More steady, a little smarter; graduated ahead of the patient
	Was considered pretuberculous and was out of school for two years as an adolescent; in spite of this graduated ahead of the patient
More active socially; more with people; does favors for people	More selfish; more to himself; less interested in people
Better mixer	More satisfied to be at home
Few temper tantrums; holds resentments; carries hostility a long time; does not show it	People say he is quick tempered; lets his temper out; gets over hurts quickly
Changed jobs several times	Stayed in one job 33 years
Always close mouthed	Always close mouthed
Very active in sports	Very active in sports
Cares more for clothes; more wiry	Cares less for clothes; more husky
Occasional drinking	Occasional drinking

In summary, the patient was by far the more dynamic of the two, more aggressive, more energetic, more active, probably more successful, although in the past few years this had been canceled by the fact that the patient had been ill. Both had a certain amount of financial security, but the patient was worried about his future, although he had savings and his wife was working. The brother was a widower, and he continued to work, being in excellent health. The two men cared for each other strongly, although there had been some estrangement at different periods in their life, due to the fact that their wives did not like each other.

In spite of the fact that the patient and his brother were strikingly alike, undoubtedly there was a certain feeling of inferiority on the part of the patient because his twin was somewhat stronger physically and more alert intellectually. The patient's brother had to stay out of school for two years on account of a suspicion of tuberculosis, yet he graduated from grammar school ahead of the patient. It is quite possible that it was this feeling of comparative inadequacy that made the patient anxious to prove that he was as good as or better than his

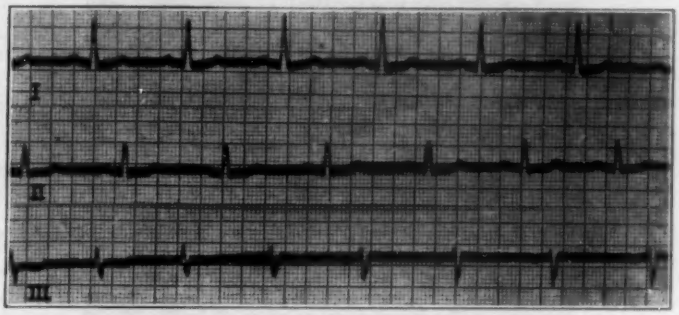

Fig. 2.—Electrocardiogram of G. G. taken in 1937, before the onset of the attacks of angina pectoris.

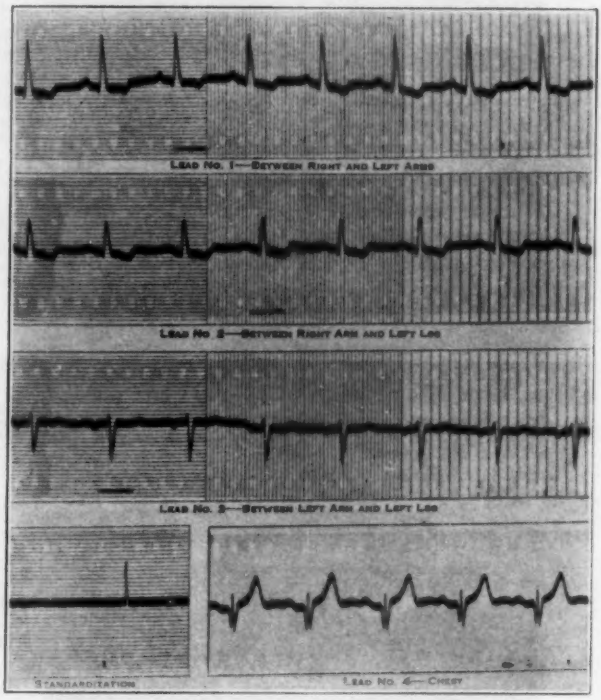
LEAD NO. 1—BETWEEN RIGHT AND LEFT ARMS
LEAD NO. 2—BETWEEN RIGHT ARM AND LEFT LEG
LEAD NO. 3—BETWEEN LEFT ARM AND LEFT LEG
STANDARDIZATION
LEAD NO. 4—CHEST

Fig. 3.—Electrocardiogram of G. G. taken in 1940, approximately one year after the onset of the attacks of angina pectoris.

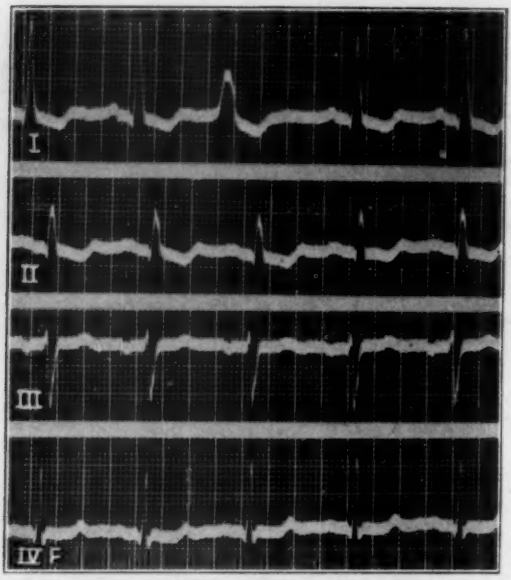

Fig. 4.—Electrocardiogram of G. G. taken on Dec. 20, 1941.

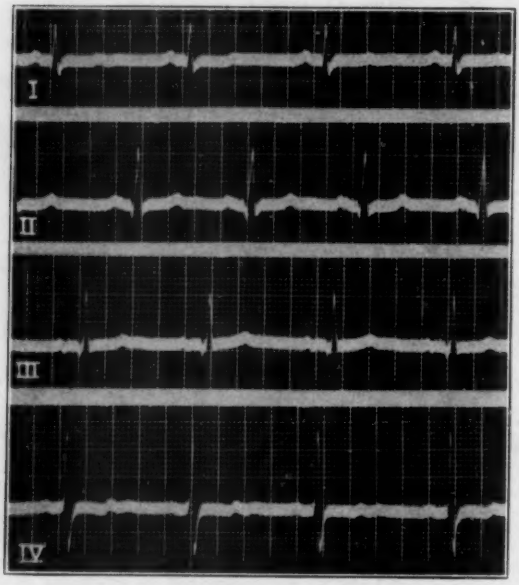

Fig. 5.—Electrocardiogram of R. G., the patient's normal brother, taken on Dec. 20, 1941.

brother and made him change jobs, take different positions and take on work entailing more responsibility and greater compensation. The most important primary difference, however, lies in the fact that the patient had always been a person who tried to please everybody and was always at every one's beck and call, never letting himself go, always suppressing his feelings, especially his hostile feelings. Franz Alexander, of Chicago, and his associates [9] have expressed strongly the belief that hostility is an important psychologic factor in the causation of hypertension. No psychologic tests were given, for with persons of this age and with their cumulative experiences such tests would not be indicative of any true difference of intelligence.

Renal Blood Flow and Inulin Clearance.—The diodrast and the inulin clearance method [10] were employed for determination of the renal blood flow and of the glomerular filtration rate respectively. The procedure followed was identical with that previously reported by one of us.[11]

It was found that the patient had a total effective renal blood flow of 606 cc. per minute. His twin brother was found to have a total effective renal blood flow of 725 cc. per minute. Both of these flows are low as compared with the average value, of 1,280 cc. per minute.[11] It should be noted, however, that there is no great difference between the two observed renal blood flows.

The similarity in the inulin clearance of the twins was even more striking, for the clearance of the patient was 97.8 cc. per minute; that of his brother was 96 cc. The filtration fraction was 21.5 per cent for the patient and 24.0 per cent for the normal twin.

Electrocardiographic Study.—The patient's first electrocardiogram (fig. 2), taken on March 4, 1937, revealed no particular abnormalities other than a low T wave in leads I and II, and complete absence of the T wave in lead III and a left axis deviation. However, the second electrocardiogram (fig. 3), taken on Aug. 29, 1940, showed unmistakable evidence of myocardial damage, strongly suggestive of disease of the coronary arteries: (1) depression of the ST segment in leads I and II, (2) inversion of the T wave in leads I and II and (3) slurring of the QRS complexes in all leads. The last electrocardiogram (fig. 4) was taken on Dec. 20, 1941 and except for the presence of an occasional ventricular extrasystole was essentially similar to the immediately preceding electrocardiogram.

The electrocardiogram of the patient's brother (fig. 5), taken on Dec. 20, 1941 on the other hand, appeared essentially normal.

COMMENT

Most recent articles concerned with renal blood flow in hypertensive persons [12] suggest the possibility that renal ischemia is not the causative agent in the pathogenesis of clinical hypertension. There is also evidence [13] that renal ischemia is not the causative agent in the pathogenesis of experimental renal hypertension.

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9. Anderson, O. D.; Parmenter, A., and Liddell, H. S.: Some Cardiovascular Manifestations of the Experimental Neurosis in Sheep, Psychosom. Med. **1**:93, 1939. Katz, L. N., and Leiter, L.: Present Conception of "Essential" Hypertension, ibid. **1**:101, 1939. Solomon, A. P.; Darrow, C. W., and Blaurock, M.: Blood Pressure and Palmar Sweat (Galvanic) Responses of Psychotic Patients Before and After Insulin and Metrazol Therapy, ibid. **1**:118, 1939. Alexander, F.: Psychoanalytic Study of a Case of Essential Hypertension, ibid **1**:139, 1939 Saul, L. J.: Hostility in Cases of Essential Hypertension, ibid. **1**:153, 1939. Miller, M. L.: Blood Pressure Findings in Relation to Inhibited Aggressions in Psychotics, ibid. **1**:162, 1939. Alexander, F.: Emotional Factors in Essential Hypertension, ibid. **1**:173, 1939.

10. Smith, H. W.; Goldring, W.; Chasis, H., and Ranges, H. A.: Observations on the Effective Renal Blood Flow and Functional Excretory Mass in Man with Especial Reference to Essential Hypertension, Am. J. Physiol. **123**:189, 1938.

11. Friedman, M.; Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Hypertension, J. A. M. A. **117**:92 (July 12) 1941.

12. Chesley, L. C., and Chesley, E. R.: Renal Blood Flow in Hypertensive Women, J. Clin. Investigation **19**:475, 1940. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow in Subjects with Hypertension, ibid. **20**:637, 1941. Friedman, Selzer and Rosenblum.[11]

13. Corcoran, A. C., and Page, I. H.: Renal Blood Flow in Experimental Hypertension Due to Constriction of the Renal Artery, Am. J. Physiol. **133**:248, 1941. Friedman, M.; Sugarman, H., and Selzer, A.: The Relationship of Renal Blood Pressure and Blood Flow to the Production of Experimental Hypertension, ibid. **134**:493, 1941.

The finding of renal ischemia of approximately the same degree in identical male twins with hypertension present in only one of them further suggests the probability that renal ischemia is an incidental factor, not a causative one, in the pathogenesis of clinical hypertension; otherwise both twins would have been hypertensive.

The clearcut demonstration of electrocardiographic and clinical signs of coronary artery disease in one of a pair of identical twins does not exclude the possibility of coronary artery disease in the apparently well twin brother. For both may have had a basic involvement of the coronary vasculature, but the fortuitous occurrence of thrombosis in but one of the twins may have given rise to the signs and symptoms observed in the patient.

It is possible, too, that the long-standing hypertension in the patient may have led to advanced degeneration of the coronary arteries. Certainly, the facts available are not sufficient to permit a certain conclusion as to the degree of underlying sclerosis of the coronary arteries in each of the twins.

A description of the contrasting personalities of these identical male twins has been included in this report because, other than the cardiovascular differences noted, they composed the only striking difference observed. Whether the lifelong existence of extreme tension and drive in the patient bore a causal relation to his hypertension is, of course, the problem. Certainly the similarity in the heredity and early environment of these identical twins stresses the divergency in personality drives as a possible cause of the hypertension found in one of them.

CONCLUSIONS

Only one of a pair of identical twins had hypertension and coronary artery disease.

Determinations of renal blood flow and of glomerular filtration were performed on both the normotensive and the hypertensive twin. The renal blood flow was found to be similarly reduced in both twins. The glomerular filtration rates also were similar.

Electrocardiograms of the patient showed evidence of myocardial damage, while a tracing made for his brother was normal.

The evidence suggests that psychologic factors may have been of primary significance in the production of hypertension in the affected twin.

Dr. Tom Addis, of Stanford University, looked over the manuscript.

Mount Zion Hospital.

MYOCARDITIS IN BRONCHIECTASIS

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Inflammatory disease of the lung is not commonly associated with myocarditis. White [1] remarked that pneumonia, either lobar or bronchial, may prove a great strain on an already weakened or diseased heart but that it does not itself cause serious heart disease except in rare circumstances. In a general study of 240 cases [2] of myocarditis the disease was found to be associated with lobar pneumonia 7 times and with bronchopneumonia 19 times. If one considers the frequency of pneumonia, these figures are not high. However, in pursuing the study of myocarditis it was noted that myocarditis was associated relatively more frequently with bronchiectasis than with uncomplicated pneumonia. This was the more noteworthy since the relevant literature barely mentions myocarditis in relation to bronchiectasis. Because myocarditis associated with bronchiectasis has been given little attention, it was considered of interest to bring forward certain facts gleaned from a study of the heart in a number of cases of bronchiectasis, in the hope that from a study of the clinical records and anatomic changes of the heart some data might be elicited concerning myocarditis, which, in general, is a rarely observed clinical entity uncommonly confirmed at postmortem examination.

As mentioned before, there are few references available on this subject. Occasional statements, however, are found ascribing death to heart failure. Jex-Blake [3] merely mentioned that 3 of 110 patients with bronchiectasis died of heart failure. Moll [4] referred to 4 patients out of 55 who died as a result of heart failure. Neither author gave any details as to the type of heart disease responsible for the 7 deaths. Ogilvie,[5] more recently, stated that myocardial damage occurs as a late result of chronic sepsis but is infrequently the direct cause of death. Wiese,[6] in a review of bronchiectasis, made no mention of heart disease as a complication. Merklen [7] observed a patient with long-standing bronchiectasis and rheumatic heart disease in whom a subacute bacterial endocarditis eventually developed.

Among 6,257 patients who came to autopsy, 152 were found to have bronchiectasis, and in 8 there was associated myocarditis. Among the 152 patients with bronchiectasis, there were 14 less than 8 months old. One of these children had myocarditis. In the following concise abstract clinical data pertinent only to the cardiovascular apparatus of the 8 patients with myocarditis are given.

Aided by a grant from the Otto Baer Fund.

From the Department of Pathology, Michael Reese Hospital. The department is in part supported by the Michael Reese Research Foundation.

1. White, P. D.: Heart Disesae, ed. 2, New York, The Macmillan Company, 1937.

2. Saphir, O.: Myocarditis: A General Review, with an Analysis of Two Hundred and Forty Cases, Arch. Path. **32**:1000 (Dec.) 1941; **33**:88 (Jan.) 1942.

3. Jex-Blake, A. J.: A Lecture on Bronchiectasis, Brit. M. J. **1**:591, 1920.

4. Moll, H. H.: A Clinical and Pathological Study of Bronchiectasis, Quart. J. Med. **1**:457, 1932.

5. Ogilvie, A. G.: The Natural History of Bronchiectasis, Arch. Int. Med. **68**:395 (Sept.) 1941.

6. Wiese, O.: Die Bronchiektasenkrankheit, Zentralbl. f. d. ges. Tuberk.-Forsch. **46**:113, 1937.

7. Merklen, P.: Dilatazione bronchiale e insufficienza mitralica, Gazz. d. osp. **54**:200, 1933.

CLINICAL DATA

The ages of these patients were 5 weeks and 33, 42, 47, 48, 55, 67 and 77 years respectively. There were 3 females and 5 males. The 5 week old infant (case 1) had congenital bronchiectasis, and collapse occurred when a thoracentesis was performed. The temperature ranged from 98 to 104 F. The 33 year old man (case 2) had had symptoms of bronchiectasis for a number of years and entered the hospital because of headaches and weakness. There was gradual development of signs of meningitis, which was thought to be the result of a cerebral abscess secondary to the bronchiectasis. Several days before he died cyanosis and tachycardia were noted. The heart was not enlarged, and the rhythm was normal. The pulse rate varied from 100 to 124; the temperature varied from 99 to 103 F.; the arterial blood pressure was 160 systolic and 105 diastolic. The 42 year old woman (case 3) had an old history of tuberculosis of the lungs with resulting bronchiectasis. Toward the end of her stay in the hospital cyanosis and dyspnea developed. Her temperature was always about 100 F., the pulse rate 105, and the arterial blood pressure 106 systolic and 64 diastolic. Clinically the heart was enlarged. The disease of the 47 year old woman (case 4) was diagnosed as bronchiogenic carcinoma. While in the hospital she became dyspneic and cyanotic and tachycardia developed. The heart was enlarged, and a soft apical systolic murmur was heard. At that time the pulse rate was 136 per minute, while the temperature was 99 F. Before death the pulse became irregular. This was the only patient in the series for whom a diagnosis of myocarditis was made. The 48 year old man (case 5), who gave a history of old bronchiectasis, began to have headaches after an apparently insignificant trauma. After a few fainting spells, he died rather suddenly. Because of the trauma and sudden death, the case was referred to the coroner. At autopsy meningitis was found, in addition to the old bronchiectasis and the acute myocarditis. The 55 year old man (case 6) gave a history of old, unresolved pneumonia, nineteen years before. On examination he was cyanotic and had edema of both lower extremities. The heart was enlarged, and the heart sounds were distant. The temperature was 99 F., the pulse rate 104 per minute and the arterial blood pressure 100 systolic and 70 diastolic. For the 67 year old man (case 7) a clinical diagnosis of bronchiectasis associated with coronary arteriosclerosis (thrombosis?) and a myocardial infarct was made. The diagnosis was confirmed at autopsy. The heart rate was rapid and the rhythm regular. The temperature was around 101 F.; the pulse rate varied but usually was 128 per minute, and the arterial blood pressure varied from 142 systolic and 76 diastolic to 110 systolic and 74 diastolic. There were three electrocardiograms. The first only is shown here (fig. 1). The heart rate was 107. The P-R interval was 0.18 second. The QRS complex was upright in the limb leads, and small in lead III with a Q wave present. There was an S wave present in lead I. The P wave in lead I was relatively small, and the P waves in leads II and III were tall and peaked. The ST segments in leads I and II were isoelectric. The ST segment in lead III was slightly elevated. The T waves in leads I and III were small and the T wave was upright in the limb leads. The QRS complex in lead CF_2 was almost entirely down, and the T waves in leads CF_2 and CF_4 were inverted. The interpretation by Dr. L. N. Katz was as follows: There was sinus tachycardia. This is a definitely abnormal record. The P waves suggest P-pulmonale. The QRS complex in lead CF_2, the Q wave in lead III and the inversion of T in the chest leads suggest an atypical coronary pattern resembling anterior wall infarction. It was decided after the record was made that another should be taken in forty-eight hours

to rule out a recent myocardial infarction. (In lead CF_4 an auricular premature systole was found; this is not shown in the illustration.)

Another record was made in forty-eight hours and still another in another forty-eight hours. They revealed some evolution, chiefly in the chest leads. This consisted of T becoming upright in these leads. At the same time a persistent auricular flutter with irregular conduction varying from 2:1 to 3:1 was present, and in the later record this was replaced by a regular 2:1 conduction. The evolution in these three records was not typical of a recent myocardial infarction, and the diagnosis was therefore entertained of an old myocardial infarction of the anterior wall with chronic coronary insufficiency and a temporary exacerbation at the time of the record shown in the illustration.

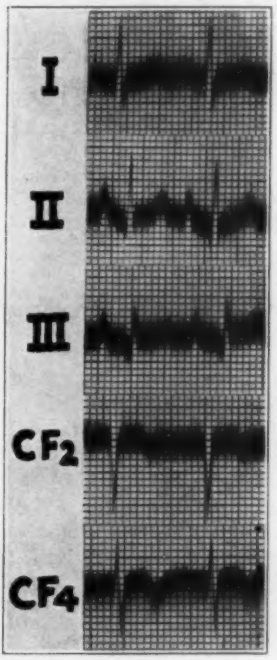

Fig. 1.— First electrocardiogram taken in case 7.

The 77 year old man (case 8) had diabetic gangrene of a lower extremity, for which the leg was amputated. The heart was enlarged, and the heart tones were fairly clear. The temperature was about 100 F., the pulse rate 128 per minute and the arterial blood pressure 170 systolic and 105 diastolic. He died rather unexpectedly following the amputation.

AUTOPSY DATA

At autopsy bronchiectasis was found in every instance. The lungs of the 5 week old infant (case 1) gave evidence of the congenital form of bronchiectasis. The 47 year old woman (case 4) had bronchiogenic carcinoma with bronchiectasis in other portions of the lung, and the 42 year old woman (case 3) had severe ulcerating tuberculosis of the lung with much fibrosis and involvement of the bronchi and

diffuse bronchiectasis. The remainder of the patients showed evidence of old or recent inflammatory disease in the lung in addition to the bronchiectasis.

The heart was enlarged in all patients with the exception of the infant and the patient who had the bronchiogenic carcinoma (case 4); the heart of the latter weighed 265 Gm. In the remainder of the 8 patients, the hypertrophy was more prominent in the right ventricle. The heart of the patient whose disease was diagnosed clinically as myocardial infarction revealed an old aneurysm of the left ventricle, involving the apex and the adjacent interventricular septum. Frank areas

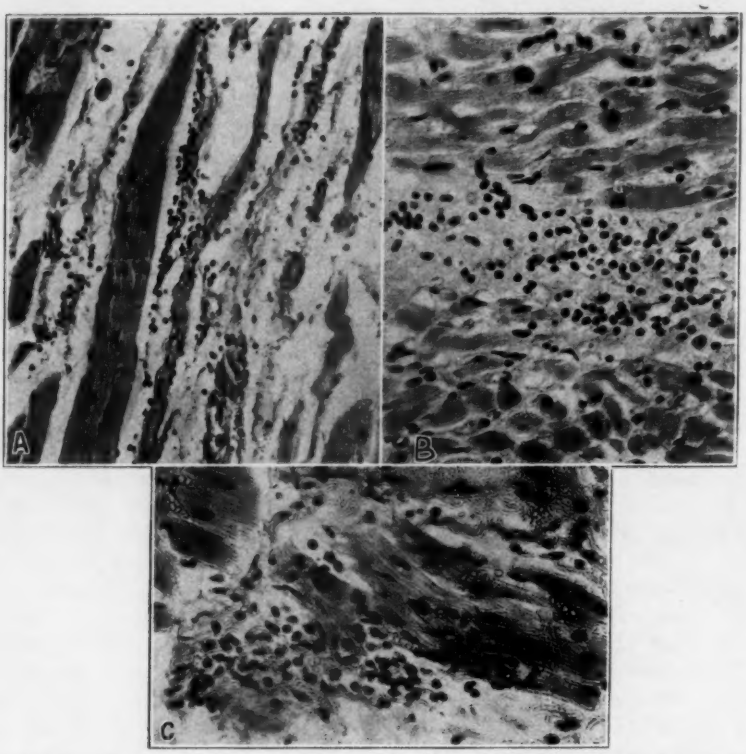

Fig. 2.—Myocarditis. *A* shows the presence of lymphocytes and a few polymorphonuclear leukocytes in the interstitial tissue (iron-hematoxylin-eosin preparation; ×120); *B*, lymphocytes and old connective tissue in the interstitial tissue space (hematoxylin-eosin preparation; ×260); *C*, lymphocytes and an occasional polymorphonuclear leukocyte in part in the interstitial tissue and in part replacing heart muscle fibers (iron-hematoxylin-eosin preparation; ×280).

of fibrosis undoubtedly the result of coronary arteriosclerosis were found in 2 additional instances.

Grossly, myocarditis was not recognized in a single instance, though a diagnosis of cloudy swelling of the myocardium was made on all the hearts. On histologic examination, however, the existence of myocarditis was obvious.

On microscopic examination in case 1 many neutrophilic polymorphonuclear leukocytes were seen extending through the entire wall of the myocardium but particularly pronounced in the right ventricle. There was also an acute pericarditis.

In case 2 the inflammatory cells consisted principally of mononuclear cells, particularly pronounced in the perivascular spaces. An occasional polymorphonuclear leukocyte and a few fibroblastic cells were also noted. In case 3 a distinctly edematous material was found in the interstitial tissue, and many polymorphonuclear leukocytes and lymphocytes were noted. No tubercles were recognized, nor did the Ziehl-Neelsen stain reveal any acid-fast bacilli. In case 4 the myocardium showed an increase in connective tissue throughout, and between the interstitial tissue fibers lymphocytes and endothelial leukocytes were noted. The vessels on section showed no change. The myocardial changes were interpreted as true chronic myocarditis. In case 5 there were disclosed a number of neutrophilic polymorphonuclear leukocytes, mononuclear cells and occasional plasma cells. These cells were found in the interstitial tissue but also could be made out replacing some heart muscle fibers. Bacterial stains showed the presence of intracellular and extracellular gram-positive cocci. The heart of patient 6, who was classified clinically as dying from myocardial failure, showed a new formation of connective tissue situated diffusely between the muscle fibers, and lymphocytes, endothelial leukocytes and a few plasma cells were found distributed throughout the newly formed connective tissue. The coronary arteries showed no sclerotic lesion. These changes were interpreted as chronic myocarditis. In case 7 sections of the myocardium showed an old myocardial infarction which was found on gross examination. Other areas of fibrosis were also noted. However, in a number of other sections neutrophilic polymorphonuclear leukocytes, lymphocytes and large mononuclear cells were seen distributed throughout the interstitial tissue. There was no evidence of recent infarction in these regions. In case 8 old connective tissue fibers were seen, partially replacing muscle fibers and partially situated in perivascular spaces. Because of the moderate coronary arteriosclerosis, these changes were interpreted as being the result of a vascular disturbance. However, in addition, a number of foci of polymorphonuclear leukocytic infiltration were noted in perivascular spaces and extending along the interstitial tissue. An occasional lymphocyte and a few plasma cells were also seen. Thus, in addition to the fibrosis of the myocardium, a recent myocarditis was encountered.

In summary, a recent myocarditis was encountered in 3 cases (cases 1, 3 and 5). Complicated with myocardial fibrosis because of coronary arteriosclerosis, recent myocarditis was found in 1 instance (case 8) and coincidental with an aneurysm of the heart in another instance (case 7). Subacute myocarditis was encountered once (case 2) and true chronic myocarditis twice (cases 4 and 6).

COMMENT

It is noteworthy that clinically the diagnosis of myocarditis was made in only a single instance (case 4). The diagnosis was arrived at because of the enlarged heart and the high pulse rate, which eventually became irregular in the face of the only slightly elevated temperature (99 F.). In retrospect, such a discrepancy between pulse rate and temperature was definitely noted in 3 patients. There were 2 other patients who perhaps had a slight discrepancy between temperature and pulse rate which may be significant in this respect (case 6, temperature 99 F., pulse rate 112; case 7, temperature 101 F., pulse rate 128). One of these patients (case 6), the 55 year old man, was considered clinically to have died of heart failure. The heart was enlarged; the heart sounds were distant, and there were edema of the lower extremities and cyanosis. The heart at autopsy showed minimal coronary arteriosclerosis, but marked myocardial fibrosis with a number of inflammatory cells was still clearly recognizable. This was 1 of the 2 instances in which a diagnosis of true chronic myocarditis was made. There was nothing else found in

the records of all these patients that could be construed as evidence in favor of the diagnosis of myocarditis. It must of course be realized that these data were taken from the records of the relevant patients and that these patients were not examined with a view to either ruling out or confirming myocarditis.

Three of the 8 patients died unexpectedly. Sudden death of patients with myocarditis is often stressed.[2] Reference will be made here only to the report of Lisa,[8] who reviewed the autopsies on 41 patients who died suddenly. In 36 of these there was acute myocarditis.

Histologically the myocardial lesions were not characteristic in any respect. The inflammatory cells were found in the interstitial tissue but also replaced occasional muscle fibers. The involvement of the interstitial tissue, however, was more pronounced. Though neutrophilic polymorphonuclear leukocytes predominated in the cases of more recent involvement, other types of inflammatory cells were noted. A predominance of eosinophilic cells was not present. In the hearts considered as showing true chronic myocarditis, there was much newly formed connective tissue, with a majority of lymphocytic cells. The Wassermann reactions of the patients were negative, and nothing was found at autopsy from which a diagnosis of syphilis could possibly be inferred.

The cause of the myocarditis in some of these instances, in which there were no other infections, was very likely the bronchiectasis. The suppuration, the large number of bacteria present in the dilated bronchi and the acute and chronic inflammation of the wall of the bronchi can easily constitute the primary focus to which the myocarditis may be ascribed. Yet in only 1 instance were bacteria found in the myocardium (case 5). In not a single instance was there an endocarditis. The chronicity of the bronchiectatic lesion may account for the subacute and chronic myocarditis in some of the cases. In a previous study [2] it was pointed out that there is little concrete evidence for the assumption that tonsillar infection may give rise to myocarditis. However, it seemed evident that more severe infections of the upper respiratory tract may occasionally cause myocarditis in the absence of endocarditis. From this study bronchiectasis and the concomitant inflammatory changes must be considered among the causes of myocarditis. It must be emphasized that it cannot be decided whether the myocarditis found in the patients with meningitis, abscess of the brain and gangrene was coincident with these lesions and possibly a manifestation of sepsis or was the direct result of the bronchiectasis.

Since, as already stated, there are very few references to myocarditis in instances of bronchiectasis, it was considered to be of interest to search for such myocardial complications in related diseases. Thus, reports of autopsies on patients dying of bronchial asthma with bronchitis were studied in this respect. It was interesting to note that such reports were very rare up to about 1930; there have been quite a few reports since that time. Though a number of authors stressed the sudden death of these patients, little attention is seemingly paid to possible microscopic changes in the myocardium, and death is ascribed to asphyxia. Fowler,[9] in reporting the sudden death of 2 such patients, stated that it is worthy of note that necropsy did not reveal any cardiac lesions which might be held responsible for the fatal outcome. Chafee, Ross and Gunn,[10] very recently, however, described a myocarditis in a patient who died suddenly after an asthmatic attack. There were massive infiltra-

8. Lisa, J. R.: Pathologic Findings in the Heart in Sudden Cardiac Deaths, Ann. Int. Med. **12**:1968, 1939.

9. Fowler, K.: Necropsy Studies on Two Patients Dying in Asthma, Pennsylvania M. J. **40**:720, 1937.

10. Chafee, F. H.; Ross, J. R., and Gunn, E. M.: Eosinophilia in Fatal Asthma: Studies of Bone Marrow and Myocardium, Ann. Int. Med. **17**:45, 1942.

tions throughout the myocardium of eosinophilic polymorphonuclear leukocytes, a few lymphocytes and plasma cells. Also encountered were small foci of necrosis. Though myocarditis was not mentioned in a second patient who also died suddenly, the description of the myocardium mentioned an infiltration by inflammatory cells. In their fifth patient, the authors again mentioned an acute nonsuppurative myocarditis.

In the autopsy files of the pathology department of Michael Reese Hospital, there are records of 3 fatal cases of bronchial asthma. The routine sections of the myocardium disclosed no inflammatory lesions. Because of the findings of myocarditis in these instances of bronchiectasis, a number of new blocks from the myocardium were cut, stained and examined. In 1 of these 3 instances evidence of myocarditis was found on a restudy of the myocardium. Thus, the question must be raised as to whether or not a careful study of the myocardiums of patients with bronchial asthma may not show myocarditis and whether this may be responsible for the sudden death not rarely encountered in these patients. It is clear that a casual microscopic examination of the myocardium cannot disclose the essential lesions. From this experience, many sections must be cut from the myocardium and the myocardium must be most carefully examined for the specific purpose of either finding or ruling out myocarditis before a negative result can be reported. This study of the myocardium in instances of bronchiectasis and bronchial asthma is significant in this respect.

SUMMARY

A type of myocarditis occurs in patients with bronchiectasis. It was found at autopsy 8 times among 152 patients and caused unexpected death 3 times. Clinically myocarditis was diagnosed in only 1 instance. The most significant clinical observation in these patients was a discrepancy between the relatively slight elevation of temperature and the high pulse rate. Bronchiectasis with the incumbent severe inflammatory changes constitutes a primary focus to which myocarditis can be ascribed. Also in some patients with bronchial asthma who die suddenly, myocarditis may be a contributory cause of the sudden death. From this study it is clear that in many instances a correct diagnosis as to the presence or absence of myocarditis can be made only if many sections are cut from the myocardium, and most carefully examined for the specific purpose of either finding or ruling out myocarditis.

PERNICIOUS ANEMIA IN NEGROES

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AND
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Pernicious anemia is said to be rare in Negroes. Our review of the last 1,000 consecutive patients with pernicious anemia who entered the Cook County Hospital contradicts this observation. This study covers the period from 1931 to 1942, during which 93 Negroes were found to have pernicious anemia. An analysis of the results of our review constitutes the subject matter of this paper.

REVIEW OF THE LITERATURE

One hundred and six cases (5 doubtful) of pernicious anemia in Negroes are reported in the literature. All the reports are by American authors and 14 of the cases have been reported from the Cook County Hospital by Carr [1] and by Traut.[2] It is noteworthy in this connection that Carr's report, which covered the period from 1912 to 1920, included only 6 cases and Traut's, based on the statistics from 1920 to 1926, only 8. These occurred in a total of 390 cases of pernicious anemia observed during this fourteen year period. Since then, perhaps because of a greater interest in pernicious anemia stimulated by the introduction of liver therapy, the diagnosis has been made annually in about three times as many cases. This only partially represents a real increase in the number of cases, since in recent years greater numbers of patients have been admitted to the hospital. Moreover, there is an increase in the life span of patients, and some of them have outlived their first or second relapse by virtue of therapy previously administered elsewhere. Nonetheless, we feel that increased awareness and more frequent recognition are mostly responsible for the threefold increase.

The previously reported cases are summarized in table 1.

Note must be taken of the fact that we deal in this entire series with North American Negroes. Previous writers have almost without exception emphasized the probability of admixture with Caucasian blood. Evans [3] particularly stressed the fact that the 9 patients on whom he reported were all mulattoes. This in no way invalidates our observations, since for practical purposes it is not possible in most instances to ascertain with any degree of certainty the presence or degree of admixture. With few exceptions our patients had the typical dark skin, dark eyes, kinky hair and negroid facies typical of the full-blooded Negro. We fully realize that this in no way excludes even a 50 per cent admixture of white blood. We feel that even if contrary observations were reported from native Negro habitats they would in no way vitiate our findings, since the adaptation of these people to a new mode of living has made them comparable to the Caucasians. Moreover,

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From the Department of Medicine, Cook County Hospital.
This work was aided by a grant from The Wilson Laboratories, Chicago.
1. Carr, J. G.: Pernicious Anemia, Am. J. M. Sc. **160**:737, 1920.
2. Traut, E. F.: Pernicious Anemia in the Negro, Illinois M. J. **51**:322, 1927.
3. Evans, F. A.: Pernicious Anemia, Baltimore, Williams & Wilkins Company, 1926, p. 28.

from a practical standpoint the question is purely academic, since the North American Negro belongs to a hybrid group. For these reasons we have made no attempt to classify our patients as more or less negroid.

Diagnostic criteria in no way differed from those well established for the disease, i. e., typical hematologic data (macrocytic anemia with high color index and characteristic changes in the red cells, leukopenia, granulocytopenia, and thrombopenia),

TABLE 1.—*Summary of Published Reports of Cases of Pernicious Anemia in Negroes*

Author and Reference	Source of Material	Year	Total Admissions	Admissions of Negroes	Total Cases of Pernicious Anemia	Pernicious Anemia in Negroes
Carr [1]	Cook County Hospital, Chicago	1912-1920	.....	"At least" 10% of total	148 (14*)	6
Jamison, S. C.: South. M. J. **19**: 583, 1926	Charity Hospital, New Orleans	1920-1926	122,524	49,188	54	12
Evans [2]	Johns Hopkins Hospital, Baltimore	1889-1922	.....	34,280	578	9 (all mulattoes)
Traut [3]	Cook County Hospital, Chicago	1920-1926	.....	"32% of total"	256	8
Mathews, H. O.: U. S. Vet. Bur. M. Bull. **5**: 494, 1929	U. S. Veterans Hospital, Tuskegee, Ala.	1923-1928	4,940	4,940	2 (1*)	2 (1*)
Gates, L. R.: A Study of Pernicious Anemia, Thesis, University of Michigan Graduate School, 1932, p. 83	University of Michigan and Simpson Memorial Institute, Ann Arbor, Mich.	1925-1932	112,290	.....	580	2
Friedlander, B. D.: Am. J. M. Sc. **187**: 634, 1934	Peter Bent Brigham Hospital, Boston	1913-1933	80,415	4,508	500	3
Strauss, N., and LaPorte, T. F. V.: New York State J. Med. **34**: 1027, 1934	Morrisania Hospital, Morrisania, N. Y.	1929-1934	.....	8,527	1	1
Kampmeier, R. H., and Cameron, P. B.: Am. J. M. Sc. **192**: 751, 1936	Charity Hospital, New Orleans	1926-1936	624,563	247,239	116 (4*)	14 (4*)
Millett, J.: Bull. School Med. Univ. Maryland **22**: 105, 1938	Meadowbrook Hospital, Hempstead, N. Y.	1935-1936	.....	.....	1	1
Granady, J. T. W.: J. Nat. M. A. **29**: 9, 1937	Private cases	.....	.....	.....	4	4
Murphy, W. P.: Anemia in Practice, Philadelphia, W. B. Saunders Company, 1939, p. 194	Private cases	1925-1938	.....	.....	578	5
Jones, C. A.: Internat. Clin. **3**: 268, 1939	Graduate School University of Pennsylvania, Philadelphia	1930-1939	.....	.....	34	21
Harvard Medical School: New England J. Med. **222**: 734, 1940	Peter Bent Brigham Hospital, Boston	1940	.....	.....	1	1
McCracken, J. B.: J. M. A. Georgia **30**: 49, 1941	Grady Hospital, Atlanta, Ga.	1935-1940	.....	46,996	59	3
Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, p. 311	Johns Hopkins Hospital, Baltimore	1925-1940	.....	⅛	329	32

* Doubtful cases.
† These two had allergy. There may have been more Negroes.

achylia gastrica, symptoms referable to the anemia and to the gastrointestinal and the nervous system specific response to the administration of liver extract and in doubtful cases a megaloblastic marrow. It may be stated parenthetically that the blood of Negroes with pernicious anemia shows changes in the red cells much more exaggerated than those seen in Caucasians.

ANALYSIS OF CASES (TABLE 2)

Relative Incidence in White Persons and Negroes.—During the period of the study approximately 800,000 patients were admitted to the hospital, of whom

200,000 were cared for in the medical wards. There were 1,000 patients with pernicious anemia among these, 93 being Negroes, which makes the ratio of white persons to Negroes about 10:1. Since white patients outnumbered the Negroes 2:1, the corrected ratio would be approximately 5:1, or 20 per cent. These figures correspond to an incidence of about 170 cases per hundred thousand among white persons and 36 cases per hundred thousand among Negroes.

Using the figures from table 1 when sufficient information is available, we find the following facts:

Of 426,500 white patients, 637 had pernicious anemia—a rate of about 150 per hundred thousand. Of 306,000 Negroes, 31 had pernicious anemia—a rate of about 10 per hundred thousand. The incidence of pernicious anemia in Caucasians seems to be fairly constant, but there is considerable discrepancy between our statistics on Negroes and those of others. In our series the occurrence in Negroes is about three and a half times as frequent as would be expected from previously reported figures.

TABLE 2.—*Age, Sex and Color Incidence Among One Thousand Patients with Pernicious Anemia* *

Age	Male		Female		Percentage Among the White Persons	Percentage Among the Negroes	Percentage in the Whole Group
	White	Negro	White	Negro			
10-19	...	..	2	..	0.2	....	0.2
20-29	2	3	6	5	0.9	8.5	1.6
30-39	33	3	30	8	7.0	11.8	7.7
40-49	72	9	69	14	15.6	24.7	16.5
50-59	123	11	130	9	28.1	21.7	27.5
60-69	143	8	119	13	29.1	22.5	28.3
70-79	69	6	82	4	16.8	10.8	16.1
80-89	10	..	11	..	2.3	....	2.1
Totals	452	40	449	53	100.0	100.0	100.0

* There were 2 Chinese males, aged 55 and 60; 3 Mexican females, aged 34, 37 and 43, and 1 Hindu male, aged 35.

Male : Female Ratio.—Of the 93 patients, 40 were males and 53 were females. Since female patients admitted are in a 3:5 minority, correcting for this would give an even greater female dominance. During a similar period the ratio in the white population was almost exactly 1:1, according to uncorrected data.

Age Incidence.—More than two thirds of the patients (64) were between the ages of 40 and 70, without a significant peak in the distribution curve. In this group the percentage distribution was essentially the same as that seen in the general population. At the age extremes, however, two interesting differences were noted. There were many more patients below 40 and far fewer over 70 among Negroes than among Causasians. The first difference is probably due to the earlier precipitation of the manifestations of pernicious anemia because of the generally poorer diet, while the second could be attributed to a shorter expectancy of life.

SUMMARY AND CONCLUSIONS

Ninety-three cases of pernicious anemia in Negroes were encountered among a total of 1,000 cases of pernicious anemia reviewed.

Pernicious anemia in Negroes occurs at the rate of 36 per hundred thousand hospital admissions, contrasting with the rate of 170 per hundred thousand in Caucasians.

The incidence of pernicious anemia is apparently somewhat higher in Negro females than in males.

The age distribution among Negroes is essentially similar to that seen among Caucasians, with two significant differences: (*a*) greater incidence in youth and (*b*) lower incidence in old age.

The pernicious anemia observed in Negroes is identical with that observed in Caucasians.

Pernicious anemia in Negroes is more frequent than previous reports would indicate, and its apparent incidence will increase as less and less emphasis comes to be placed on its rarity.

1825 Harrison Street.

SPLENOPORTAL VENOUS OBSTRUCTION WITHOUT SPLENOMEGALY

FURTHER CONTRIBUTION TO THE PATHOGENESIS OF FIBROCONGESTIVE SPLENOMEGALY (BANTI SYNDROME)

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It has been proved beyond a reasonable doubt that the Banti syndrome, a morbid condition characterized by chronic fibrous and congestive splenomegaly, secondary anemia and recurrent hematemeses, may occur independently of any obstruction to the portal circulation.[1] The splenic enlargement thus is not the result of circulatory disturbances in the portal bed, though portal sclerosis and thrombosis may secondarily complicate the picture. A drawback to the general acceptance of this concept lies in the fact that the same clinical and pathologic picture occurs in instances in which the presence of an important obstacle in the portal vessels suggests that the mechanism is passive hyperemia of the spleen. Depending on the nature of the obstruction in individual cases, this condition is termed thrombophlebitic splenomegaly,[2] portal phlebosclerosis [3] or cavernomatous transformation of the portal vein.[4] The current assumption [5] that the splenomegaly is primary in some instances and secondary in others would seem to offer a compromise which is not too convincing. On the other hand, the assumption that all these splenomegalies are secondary, even in the absence of an obstruction, is not acceptable, for the existence of a primary fibrocongestive splenomegaly is well established.

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From the Department of Pathology, Michael Reese Hospital, Chicago. The department is in part supported by the Michael Reese Research Foundation.

1. Ravenna, P.: Banti Syndrome (Fibrocongestive Splenomegaly): Definition, Classification and Pathogenesis, Arch. Int. Med. **66**:879 (Oct.) 1940.

2. (*a*) Dévé, F.: Splénomégalie chronique avec anémie d'origine pyléthrombosique, Normandie méd. **23**:109 (March) 1908. (*b*) Cauchois, A.: Splénomégalies chroniques d'origine pyléthrombosique, Thesis, Paris, no. 422, Paris, G. Steinheil, 1908. (*c*) Warthin, A. S.: The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anemia and Banti's Disease, Internat. Clin. **4**:189, 1910.

3. (*a*) Simmonds, M.: Ueber Pfortadersklerose, Virchows Arch. f. path. Anat. **207**:360, 1912. (*b*) Winkler, H.: Ueber primäre Pfortaderthrombose bei Pfortadersklerose und bei chronischen Milz-tumor, Frankfurt. Ztschr. f. Path. **17**:377, 1914. (*c*) Wohlwill, F.: Ueber Pfortadersklerose und Bantiähnliche Erkrankungen, Virchows Arch. f. path. Anat. **254**:243, 1925. (*d*) Freund, M., and Schick, B.: A Typical Form of Splenomegaly in Children: Phlebosclerosis of the Portal Circulation, J. Mt. Sinai Hosp. **4**:221 (Nov.-Dec.) 1937.

4. Klemperer, P.: Cavernomatous Transformation of the Portal Vein: Its Relation to Banti's Disease, Arch. Path. **6**:353 (Sept.) 1928.

5. (*a*) Davies, J. C.: Splenic Anaemia and Portal Thrombosis, Lancet **2**:498 (Sept. 8) 1928. (*b*) Villa, L.: Zur Diagnose der Milzvenenthrombose, Med. Klin. **25**:909 (June 7) 1929. (*c*) Moretti, E.: Sindromi splenoepatiche e splenomegalia tromboflebitica (Contributo anatomo-clinico), Arch. di pat. e clin. med. **7**:511 (Nov.) 1928. (*d*) Frugoni, C.: La splenomegalia tromboflebitica primitiva, ibid. **3**:574 (Dec.) 1924. (*e*) Brandberg, R.: Untersuchungen über splenomegale Leberzirrhosen, sog. thrombophlebitische Milztumoren und chronischinfektiöse Milzvergrösserungen unter besonderer Berücksichtigung der Pathogenese und der Behandlungsresultate bei Splenektomie, Acta chir. Scandinav. (supp. 40) **77**:1, 1935. (*f*) Dameshek, W.: Medical Progress: Hematology, New England J. Med. **224**:729 (April 24) 1941.

Rather it seems that the evidence in favor of the occurrence of a splenomegaly caused entirely by passive hyperemia should be critically reexamined.

In an earlier study [6] an attempt was made to show that, while the majority of cases reported in the literature as instances of thrombophlebitic splenomegaly should be considered cases of primary splenomegaly complicated by thrombophlebitis, definite evidence for ruling out the possibility that isolated splenic enlargements depended on a primary venous occlusion was still missing. It seems that the solution of this problem lies in the demonstration of splenomegaly entirely due to passive hyperemia. In search of such evidence, the autopsy protocols of Michael Reese Hospital, in Chicago, covering autopsies performed between 1909 and December 1942 were investigated. Cases were chosen in which there was absolute certainty that the venous occlusion was not the result of splenic enlargement and that if splenic enlargement was present it could not be explained as due to some other cause. Thus instances of portal thrombosis occurring in syphilitic or leukemic patients were not considered, for the splenic enlargement could be explained independently of any passive hyperemia.

CLASSIFICATION OF CASES

The most common conditions causing chronic passive hyperemia of the spleen are: (1) occlusion of the splenic or portal vein, (2) chronic heart failure and (3) cirrhosis of the liver.

Cases with Occlusion of the Splenic or Portal Vein.—In this series there were 12 cases in which occlusion of the splenic or portal vein or both was surely not dependent on a disease of the spleen. The essential data are collected in the accompanying table. In 11 cases the obstruction was due to a tumor, either directly invading the splenic or portal vein or compressing it from the outside. In 1 case a fibrous band produced a stricture of the portal vein. The weight of the spleen was normal in 7 instances, smaller than normal in 3 (respectively, 60, 90 and 100 Gm.) and slightly larger than normal in 2 (respectively, 200 and 210 Gm.). In 1 of these 2 cases there was an early hepatic cirrhosis and the enlargement of the spleen, moderate indeed, might have been due to the cirrhosis of the liver.

It is impossible to know the exact time of onset of the venous obstruction in the cases reported here. It can safely be admitted, however, that the occlusion had lasted not less than several days (since at least several days are necessary for a tumor mass to grow so as to obstruct a large vein) and that it was probably several weeks in cases in which both the portal and the splenic vein were occluded by tumor tissue or in which the thrombus showed advanced organization and possibly several months in the instance of portal constriction from an old scar. Since extremely recent occlusions were not included in this series, none of the patients presented the moderate splenic enlargement which occurs immediately after occlusion of the splenic vein but subsides in a few days.[7] Except possibly in 1 case (no. 2), the occlusions were not of very long standing. This fact does not preclude the conclusion to be drawn here, because if no enlargement is manifest within the first few weeks after the establishment of a venous occlusion it is extremely unlikely that it will develop subsequently, at a time when the formation

6. Ravenna, P.: La splenomegalia fibroso-congestizia primitiva con cirrosi epatica e la sua sistemazione fra le sindromi bantiane, Minerva med. **1**:225 (March 10); 255 (March 17); 276 (March 24); 306 (March 31) 1936.

7. Fieschi, A.: Splenotromboflebite acuta e cronica: Studio clinico e istopatologico di un caso operato precocemente e di un caso decorrente da oltre venti anni, Clin. med. ital. **70**:133 (Jan.-April) 1939.

of collateral pathways and the canalization of the occluded vessel have relieved the circulatory disturbance.

In the present material the older age group predominates, and it may be observed that in old age the spleen is less likely to expand. However, 4 patients were less than 34 years old and 1 was 45 years old, and their spleens were not larger than the others'.

The average weight of the spleen in the Banti syndrome is more than 1,000 Gm.[8] The average weight of the spleen in these cases of portal obstruction was 140 Gm. The discrepancy is so great that it is difficult to imagine that it can be explained without invoking some factor other than passive hyperemia.

Cases with Chronic Cardiac Failure.—It is common knowledge that chronic cardiac failure does not produce great and permanent enlargement of the spleen.[9]

Data on Twelve Cases of Portal Obstruction Independent of Splenic Disease

Case No.	Sex	Age	Pathologic Diagnosis	Nature of Obstruction	Weight of Spleen, Gm.	Comments
1	M	71	Carcinoma of stomach	Extension of carcinoma into portal vein; organizing thrombosis	90	Ascites, 1,800 cc.
2	M	56	Subacute peritonitis	Fibrous band around portal vein	60	Ascites, 2,000 cc.
3	F	71	Carcinoma of pancreas	Extension of carcinoma into splenic vein	100	Ascites, 600 cc. (recent paracentesis, 3,000 cc.)
4	M	64	Carcinoma of pancreas	Partial occlusion from organized thrombosis splenic vein	135	
5	F	33	Retroperitoneal chromaffin tumor	Compression of portal vein by tumor	Normal	
6	F	24	Carcinoma of rectum	Complete occlusion of splenic and portal veins by tumor; splenic vein filled up to hilus of spleen	115	
7	M	32	Carcinoma of pancreas	Obliteration of portal vein by tumor	210	Ascites, 1,500 cc. (recent paracentesis, 3,200 cc.)
8	F	50	Carcinoma of pancreas	Extension of carcinoma in portal and splenic veins	175	Ascites, 100 cc. (recent laparotomy)
9	M	28	Carcinoma of colon	Infiltration of the wall of portal vein	Normal	
10	F	61	Carcinoma of stomach	Metastasis in portal vein	Normal	
11	F	45	Primary carcinoma of liver	Carcinoma metastasis occluding portal vein	200	Early portal cirrhosis; ascites, 1,000 cc.; esophageal varices
12	M	57	Carcinoma of stomach	Occlusion of right and left branches of portal vein by tumor	175	Ascites, 2,000 cc.

On the contrary, the spleen may be reduced in size (cyanotic atrophy). These facts confirm the statement made many years ago by Oestreich[10] that the size of

8. (*a*) McMichael, J.: The Pathology of Hepatolienal Fibrosis, J. Path. & Bact. **39**:481 (Sept.) 1934. (*b*) Hu, C. H., and Chu, I. K. C.: Banti's Disease and Laennec's Cirrhosis: A Clinical and Anatomical Study with Observations on Their Possible Etiological Relationship, Chinese M. J., March 1938, supp., p. 1. (*c*) Lubarsch, C.: Pathologische Anatomie der Milzvergrösserungen, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40**:527, 1928.

9. (*a*) Rolleston, H. D., in Discussion on Splenic Enlargements Other Than Leukaemic, Brit. M. J. **2**:1157 (Oct. 17) 1908. (*b*) McNee, J. W.: Croonian Lectures on Liver and Spleen: Their Clinical and Pathological Associations, ibid. **1**:1017 (June 4); 1068 (June 11); 1111 (June 18) 1932. (*c*) D'Arrigo, S.: Milza da stasi cronica centrale, Pathologica **30**:430 (Oct. 15) 1938. (*d*) Klemperer, P.: The Spleen, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, pp. 1587-1754.

10. Oestreich, R.: Die Milzschwellung bei Lebercirrhose, Virchows Arch. f. path. Anat. **142**:285, 1895.

the spleen does not give information as to the degree of distention and stasis in the portal venous system.

Cases with Hepatic Cirrhosis.—This condition is mentioned here because it has been affirmed that the splenic enlargement of hepatic cirrhosis offers an example of chronic passive hyperemia of the spleen producing splenic enlargement. There are many arguments, however, against the assumption that this enlargement is due to passive hyperemia alone. The following are the most important: (1) splenic enlargement is frequent, but not constant even in the most advanced stages of the cirrhotic process [11]; (2) enlargement is sometimes present when the cirrhotic changes are, from a mechanical viewpoint, still insignificant [12]; (3) the microscopic appearance of passive hyperemia of the spleen is different from the histologic changes in the same organ in cases of hepatic cirrhosis [13]; (4) in experimental cirrhosis splenic enlargement preceded portal stasis [14]; and (5) enlargement occurred when the spleen was dissociated from the portal circulation and implanted in the subcutaneous tissue of the abdomen (marsupialized spleen) [15]; (6) in cases of portal cirrhosis complicated by portal thrombosis, as in the instances collected by Reich,[16] the splenic enlargement could easily be explained on the basis of the cirrhotic process alone, since it was not constant, was of moderate size and seemed to occur with the same frequency as in cases of uncomplicated hepatic cirrhosis.

Thus the results of study of the size of the spleen in hepatic cirrhosis are not contributory to the question of splenomegaly exclusively due to passive hyperemia.

COMMENT

The 12 instances of portal obstruction reported on here speak against the possibility that passive hyperemia alone may produce a splenic enlargement of long duration and of some importance. As long ago as 1908, Osler [17] remarked that neither splenomegaly nor anemia is a special feature in cases of long-standing obliteration of the portal vein. Other authors [18] reported instances of portal thrombosis not accompanied by splenic enlargement. Lack of correlation between stenosis of the portal vein and splenomegaly was noticed also by Simmonds [2a] in 7 cases.

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11. Klemperer.[9d] Lubarsch.[8c]

12. (*a*) Banti, G.: Ueber Morbus Banti, Folia haemat. **10**:33, 1910. (*b*) Cushing, H., and MacCallum, W. G.: Two Cases of Splenectomy for Splenic Anemia: Report on Pathologic Changes in Splenic Anemia, Arch. Surg. **1**:1 (July) 1920. (*c*) Oestreich.[10] (*d*) McNee.[9b] (*e*) Brandberg.[5e]

13. Jäger, E.: Milzbau und Kreislaufstörung: I. Ein Beitrag zur Entstehung von Milzveränderungen bei Stauungszuständen im Pfortadersystem, Virchows Arch. f. path. Anat. **299**:531, 1937. Oestreich.[10] Klemperer.[9d]

14. Menon, T. B.: The Splenic Reaction in Experimental Cirrhosis and in Precirrhotic Intoxication, J. Path. & Bact. **46**:521 (May) 1938.

15. Cameron, G. R., and De Saram, G. S. W.: A Method for Permanently Dissociating the Spleen from the Portal Circulation (the "Marsupialized" Spleen) and Its Use in the Study of Experimental Liver Cirrhosis, J. Path. & Bact. **48**:41 (Jan.) 1939.

16. Reich, N. E.: Portal System Thrombosis Occurring in Portal Hypertension, Ann. Int. Med. **17**:270 (Aug.) 1942.

17. Osler, W., in Discussion on Splenic Enlargements Other Than Leukaemic, Brit. M. J. **2**:1151 (Oct. 17) 1908.

18. (*a*) Christeller, E., and Puskeppelies, M.: Die peri-arteriellen Eisen- und Kalkinkrustationen in der Milz, Virchows Arch. f. path. Anat. **250**:107, 1924. (*b*) Franke, H.: Zur Diagnose der trunkulären und terminalen Pfortaderthrombose, Med. Klin. **35**:1601 (Dec. 15); 1632 (Dec. 22) 1939. (*c*) Borrman: Beiträge zur Thrombose der Pfortaderstamme, Deutsches Arch. f. klin. Med. **59**:283, 1897. (*d*) Weir, J. F., and Beaver, D. C.: Diseases of the Portal Vein: A Review of One Hundred and Twenty-Seven Instances, Am. J. Digest. Dis. & Nutrition **1**:498 (Sept.) 1934. (*e*) Lubarsch.[8c] (*f*) Wohlwill.[8c]

All these observations, however, were overshadowed by the fact that too often in the literature on portal obstruction the size of the spleen was mentioned only if there was a marked enlargement. Thus, in a study of 68 cases of occlusion of the portal vein Lissauer [19] reported the following splenic changes: leukemia in 1, perisplenitis in 2, splenic abscesses in 2 and total infarction in 1. The spleen was not mentioned in the reports of the remaining 62 cases. More recently 21 instances of portal obstruction from various causes (including 6 of obstruction due to cancer) were collected by Webster.[20] The splenic weight was given in 1 case only, in which it was 2,400 Gm. and the diagnosis of Banti's disease had been made. Incidentally, the thrombus was recent and could not have been the cause of the splenic enlargement. The size of the spleen was also not stated in 7 of 8 instances of portal thrombosis confirmed at autopsy reported by Pallette.[21] In the remaining case, in which the condition had been diagnosed as Banti's disease, the thrombus was recent and was believed to be a sequel of splenectomy. This tendency to call attention to the spleen if it is enlarged and not to mention it otherwise may be partly responsible for the general impression that portal thrombosis is a cause of splenomegaly.

A splenic enlargement of long duration could not be obtained in experimental animals by producing passive hyperemia of the spleen. Warthin's [22c] experiments were among the first. By ligation of the splenic vein in dogs and rabbits, he obtained an early enlargement, followed by permanent atrophy of the spleen. Consistently similar results were observed more recently,[22] even when the obstruction was applied progressively or intermittently. Passive hyperemia of the liver and of the portal venous system may also be obtained by ligation of the hepatic artery; even here, after an early enlargement of a few days' duration, atrophy of the spleen ensued.[23] One should therefore conclude with Menon [22a] that these experiments do not support, but seem to negate, the view that the Banti syndrome is due to blockage of the portal vein. The only discordant opinion was formulated by Rousselot and Thompson.[22b] These authors obtained a cirrhosis of the liver and a lasting splenic enlargement in dogs after repeated injections of small particles of silicon dioxide (silica) into the portal vein. However, some of the particles were eventually found in the spleen itself. Thus some direct damage to the spleen could not be ruled out, and the authors' contention that passive hyperemia alone was responsible for the splenic enlargement was not proved.

The idea that passive hyperemia alone is sufficient to produce a chronic splenomegaly was based on a mere coincidence. In most instances fibrocongestive splenomegaly was accompanied by portal venous sclerosis (Banti [24] called it endophlebitis), and this could give origin to a venous thrombosis.[25] When autopsy

19. Lissauer, L.: Beitrag zur Frage der Entstehung der Pfortaderthrombose, Virchows Arch. f. path. Anat. **192**:279, 1908.

20. Webster, L. T.: Portal Thrombosis, Bull. Johns Hopkins Hosp. **32**:16 (Jan.) 1921.

21. Pallette, E. C.: Portal Thrombosis, California & West. Med. **45**:324 (Oct.) 1936.

22. (*a*) Menon, T. B.: Venous Splenomegaly: A Study in Experimental Portal Congestion, J. Path. & Bact. **46**:357 (March) 1938. (*b*) Rousselot, L. M., and Thompson, W. P.: Experimental Production of Congestive Splenomegaly, Proc. Soc. Exper. Biol. & Med. **40**: 705 (April) 1939. (*c*) Castiglioni, G., and Pepere, M.: Ricerche sperimentali intese a modificare il circolo splenico, Arch. ital. di anat. e istol. pat. **11**:14 (Dec.) 1939.

23. Patrassi, G., and Baggio, G.: L'arteria epatica come fattore propulsivo del circolo portale: Su alcuni effetti della legatura dell'arteria epatica sugli organi splancnici, Sperimentale, Arch. di biol. **99**:361, 1939.

24. Banti, G.: La splenomegalia con cirrosi epatica, Sperimentale (sez. biol.) **48**:407, 1894.

25. Rosenthal, N.: Clinical and Hematologic Studies on Banti's Disease: I. The Blood Platelet Factor with Reference to Splenectomy, J. A. M. A. **84**:1867 (June 20) 1925. Nägeli,

was performed after the splenomegaly had lasted a number of years, the venous changes often were so pronounced that it could be easily assumed that they were the oldest and the primary lesions. It may be of interest in this respect to mention the report of Wallgren.[26] He described 4 patients with fibrocongestive splenomegaly in all of whom the portal vessels were normal. Nevertheless, being unable to explain the splenic enlargement otherwise, he postulated that a portal stenosis must have been present and described his cases as instances of "chronic splenic pylephlebostenosis."

Even when both the cause of the splenic enlargement and that of the portal obstruction are unknown, a complete pathologic examination and a consideration of the pathologic and clinical data will frequently show that the portal obstruction is not the cause of the splenomegaly. In each individual case different elements should be considered, but the venous occlusion should not be assumed to be the primary cause of the circulatory disturbance in the portal bed if: (1) the occlusion is located outside the portal or splenic vein (e. g. in the gastric or mesenteric veins) and therefore does not hinder the venous return from the spleen; (2) the occlusion is located in the splenic or portal vein but (*a*) there are large anomalous anastomoses between the splenic and the left renal vein (providing adequate collateral circulation from the spleen into the renal vein), (*b*) the occlusion is due to a thrombus situated in a dilated or clearly aneurysmal segment of the vein (which makes it likely that the vein was damaged previously and that the thrombosis is a secondary phenomenon), (*c*) the occlusion is due to a recent thrombus, while the splenomegaly is known to have lasted a long time, (*d*) the vein involved is tortuous and dilated not only distally but beyond the obstructed segment (which indicates that the portal hypertension occurred independently and probably before the venous obstruction) or (*e*) the splenic artery is dilated (this is important, since venous obstruction of any degree cannot cause dilatation of a large artery and this possibility is even more remote in the case of the spleen, for backward perfusion of this organ is impossible[27]); (3) the occlusion is due to a trauma and it is not excluded that this produced some lesions of the vasomotor nerves of the spleen, thereby causing active splenic hyperemia (this point will be discussed further in this study) or (4) there are signs of exaggerated splenic activity, such as (*a*) delayed physical development (so-called splenic infantilism), (*b*) leukopenia with relative monocytosis and lymphocytosis or/and (*c*) anemia due to depressed activity of the bone marrow or to excessive hemolysis. Increased activity of the spleen may indeed be a consequence of active hyperemia of this organ, but not of passive hyperemia.

Reviewing the literature on splenomegalies, I did not find a single instance in which the diagnosis of splenomegaly of passive hyperemia may be sustained if the aforementioned diagnostic criteria are used. In the great majority of cases the anatomic description of the vessels and organs involved is so incomplete that a critical evaluation is impossible. In a few others it can be definitely stated that

P.: Die Klinik der chronischen Megalosplenien, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40**:511, 1828. Grégoire, R.: Pyléthrombose et splénectomie, Sang **9**:761, 1935. Moiroud: Olmer, J., and Jouve, A. X.: Splénomégalie scléreuse avec gastrorragies: Splénectomie suivie de thrombose porto-mésentérique tardive, Mém. Acad. de chir. **63**:543 (April 21) 1937. Davies.[5a] Ravenna.[6] Brandberg.[5e]

26. Wallgren, A.: Contribution à l'étude des splénomégalies de l'enfance (Pyléphlébosténose splénique), Acta pædiat. (supp.) **7**:1, 1927.

27. Guillery, H., and Petersen, H.: Untersuchungen über die Funktionen der Milz: IV. Die Blutaufnahme und -abgabe und die Blutsperren der Milz, Ztschr. f. d. ges. exper. Med. **101**:683, 1937.

the diagnosis was erroneous, as for instance when the diagnosis of thrombophlebitic splenomegaly was made and the thrombus was located in the superior mesenteric vein,[28] the occluded vein was dilated beyond the obstructed segment,[29] a large anomalous anastomotic vein connected the splenic and left renal veins,[30] apparently providing adequate collateral circulation, or, finally, the splenic artery was described as greatly dilated.[31]

If all possible diagnostic criteria are used to differentiate between splenomegaly due to passive hyperemia and splenomegaly complicated by portal obstruction, I believe that in most cases the enlargement will be classified as belonging to the latter type. In a few instances it may not be possible to decide anatomically whether the portal obstruction preceded or followed the splenomegaly, and in some exceptional case it may even be clear that the portal obstruction preceded. To classify these instances properly it is well to remember that neither pathologic nor experimental evidence supports the possibility of a chronic splenomegaly exclusively due to passive hyperemia.

For instance, a case is on record [32] in which the splenic enlargement developed after a trauma which also caused constriction of the splenic vein. During splenectomy the "portal vessels" were seen to be tortuous and dilated. Since the obstruction of the splenic vein did not prevent a dilatation of the veins distal to the obstacle, it could not have had a determining effect in the production of the splenic hyperemia. Rather, it seems likely that the mechanism was a lesion (compression, severance) of the splenic nerves running alongside the splenic artery and that the consequent vasomotor paralysis produced active hyperemia of the spleen.

The assumption that the splenomegaly in Banti's syndrome may be due to a lesion of the nerves of the spleen was proposed by Barr.[33] In the autopsy protocols of Michael Reese Hospital I found the description of a case which seems to substantiate this hypothesis.

The patient was a girl who at the age of 3½ years fell out of bed and immediately afterward complained of violent abdominal pain. Two weeks later she had a sudden hematemesis, which recurred several times during the following years. When she was 11 years old an enlarged fibrocongestive spleen was removed, but the gastric hemorrhages recurred after the operation, causing death one year later. At the autopsy an eroded varicose vein near the cardiac end of the stomach was interpreted as the cause of the final hemorrhage. The mechanism of the portal

28. Lucchi, G.: Morbo di Banti a lentissimo decorso e splenomegalia tromboflebitica con trombosi della vena mesenterica superiore, Riv. di clin. med. **35**:421 (July 15) 1934.

29. Dubois-Roquebert and Sigault: Splénomégalie thrombophlébitique, Mém. Acad. de chir. **66**:295 (Feb. 28-March 6) 1940.

30. Arrigoni, A.: Anemia emolitica, secondaria a reticolo-endoteliosi sistemica, subentrante a sindrome tromboflebitica della splenica, Med. ital. **16**:531 (Aug.) 1935. Simonds, J. P.: Chronic Occlusion of the Portal Vein, Arch. Surg. **33**:397 (Sept.) 1936. Haintz, E., and Romhanyi, G.: Stenose der Vena portae mit Symptomen der Thrombose der Vena lienalis, Ztschr. f. klin. Med. **135**:66, 1938.

31. (*a*) Onsy, A. B.: The Pathogenesis of Endemic (Egyptian) Splenomegaly, Tr. Roy. Soc. Trop. Med. & Hyg. **30**:583 (April) 1937. (*b*) Olmer, J.; Vague, J., and Dumon-Legré, M.: Splénopathie cirrhogène avec calcification de la veine splénique, Ann. d'anat. path. **16**:905 (July) 1939. (*c*) Christeller and Puskeppelies.[18a] (*d*) Edens: Ueber Milzvenenthrombose, Pfortaderthrombose und bantische Krankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **18**:59, 1908. (*e*) Brahme, L.: Ein Fall von chronischen Pfortahindernis, Acta med. Scandinav. **61**:175, 1924.

32. Thompson, W. P.: The Pathogenesis of Banti's Disease, Ann. Int. Med. **14**:255 (Aug.) 1940.

33. Barr, J.: Three Cases of Banti's Disease, Lancet **2**:493 (Aug. 23) 1902.

hypertension causing the gastric varices was not explained at autopsy, for no obstacle whatsoever was seen in the portal venous system or in the liver.

The case presents a striking similarity to an instance reported by Cesa-Bianchi and Cellina.[34] Their patient was a healthy boy who at the age of 9 years fell and received a violent contusion in the abdomen. Twelve hours later he had a severe hematemesis. At that time splenomegaly and anemia with leukopenia were found. After two years of relative well-being he had a sudden hematemesis, which was followed by death. At autopsy, a fibrocongestive splenomegaly with many sclerosiderotic nodules was noted, but no obstacle to the portal flow. A few small patches of intimal thickening represented the only lesion of the portal venous system. The possibility that the trauma was responsible for a lesion of the nervous system producing splenic congestion must be seriously considered in these instances. This splenomegaly would have the same origin as the splenic enlargement obtained experimentally by denervation of the spleen.[35] A nervous mechanism might also be responsible for the splenomegaly in cases in which the disease developed in patients with adrenal deficiency.[36] This would explain the rapid and marked reduction of splenic size obtained in some instances by repeatedly injecting epinephrine hydrochloride intravenously.

In the pathogenesis of fibrocongestive splenomegaly, however, a purely nervous mechanism is probably rather infrequent. In most instances the splenic enlargement is due to toxic, infectious or parasitic damage to the splenic parenchyma itself.[1]

It is impossible to say at present how many examples of the Banti syndrome previously classified as splenomegaly caused by passive hyperemia were due to an infection of the spleen. The difficulty lies in the fact that, even in known specific infections and infestations, the finding of the etiologic agent and of inflammatory lesions in the spleen is extremely rare. The development of the knowledge of the pathogenesis of schistosomial splenomegaly offers an interesting example of the difficulties involved. This disease was called "endemic Egyptian splenomegaly," and as long as its cause was unknown it was considered identical with Banti's disease. When ova of Schistosoma were found in the livers of many patients, it was thought that the splenomegaly was the consequence of passive hyperemia due to parasitic obstruction of the portal vein. Finally, by means of more accurate and extensive research,[21a] ova were found inside the spleen itself, but in small number and showing advanced regressive changes. It was also noticed that the splenic artery was greatly dilated. Therefore it seems that, though the spleen rapidly destroys the parasite, parenchymal changes ensue, which are responsible for the splenic enlargement. Portal obstruction, which occurs rarely and late in this condition, should be a factor of little, if any, importance.

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34. Cesa Bianchi, D., and Cellina, M.: Morbo di Banti e sindromi affini, Rome, Luigi Pozzi, 1939.

35. von Tarchanoff, F.: Ueber die Innervation der Milz und deren Beziehung zur Leucocythämie, Arch. f. d. ges. Physiol. **8**:97, 1874. Henschen, C., and Howald, R.: Die anatomischen und klinisch-physiologischen Folgen der operativen Entnervung der Milz: Experimentelle Untersuchungen, Arch. f. klin. Chir. **157**:667, 1929. Barcroft, J., and Elliott, R. H. E.: Some Observation on the Denervated Spleen, J. Physiol. **87**:189 (July) 1936. Pasqualino, G.: Ricerche preliminari sulla provocazione di una possibile ipersplenia terapeutica, Biochim. e terap. sper. **25**:327 (July 31) 1938. Sugimura, M.: Ueber Milzentnervung, Arch. f. klin. Chir. **197**:169, 1939.

36. Galluppi, A.: Malattia di Banti e affezioni sistematizzate del reticolo-endotelio, Clin. med. ital. **60**:183 (May-June) 1929. Cesaris Demel, V.: Considerazioni sull'atonia dell'apparato muscolare contrattile della milza nella patogenesi di alcune splenomegalie, Baglivi **1**:200, 1935. Lenzi, F.: Sindrome bantiana: Splenomegalia fibroso-congestizia prevalentemente fibrosa (contributo clinico; ipotesi patogenetiche), Haematologica **22**:47, 1940.

SUMMARY AND CONCLUSIONS

The assumption that fibrocongestive splenomegaly may be due to passive hyperemia is not satisfactory, because it fails to explain several facts observed in this condition. Only the finding of some type of venous obstruction in a large number of cases of fibrocongestive splenomegaly seems to speak in favor of passive hyperemia as cause of splenomegaly. However, such obstruction was missing in several cases, and if present it was found in late stages of the disease. There are several often overlooked signs which may be of assistance in deciding whether the obstruction preceded or followed the onset of the splenic enlargement.

In 12 consecutive instances in which portal obstruction was surely independent of a splenic disease the spleen was not appreciably larger than normal. In 3 of them it was smaller than normal. This agrees with the observations that the experimental ligation of the splenic vein produces not enlargement but atrophy of the spleen and that chronic passive hyperemia due to cardiac failure does not cause marked enlargement of the spleen and often induces its atrophy.

It is therefore concluded that: (1) passive hyperemia alone is not sufficient for the production of chronic splenic enlargement; (2) obstruction of the portal venous circulation in cases of fibrocongestive splenomegaly represents not the cause but a complication of the splenic disease, and (3) terms such as primary splenic thrombophlebitis, phlebosclerosis, phlebostenosis, cavernomatous transformation of the portal vein with secondary splenomegaly and splenomegaly of passive hyperemia are misnomers, because they represent an erroneous conception as to pathogenesis, and should not be used. In most of the cases collected under such headings, the splenomegaly constitutes the primary change.

REVIEW OF NEUROPSYCHIATRY FOR 1943

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MOTONEURON

At the termination of every reflex arc we find a final neurone, the ultimate conductive link to an effector organ, gland, or muscle. This last link in the chain—e. g., the motoneurone—differs obviously in one important respect from the first link in the chain. It does not subserve exclusively impulses generated at one single receptive source alone, but receives impulses from many receptive sources situate in many and various regions of the body.

Thus in 1904 Sherrington [1] described the "final common path" of nervous impulses from anterior horn cell in the spinal cord to motor end plate in the striated muscle. On his work depends most of the knowledge of the reflex function of cord and muscle, and recent work is largely elaboration of what he began. During the last two years several important discoveries have been made in this field.

In the first place, Elliott [2] has shown that the distribution of the somatic motor cells of the ventral gray columns of the spinal cord is not as usually described by anatomists. These cells, which, with their axons, constitute the final common pathway to the voluntary muscles, were usually considered to have a segmental distribution even in the lumbosacral and cervical enlargements. At the center of a spinal segment there was supposed to be a mass of cells that spindled off at the limits of the segment, so that a picture of one of the cell columns would look like a string of spindle-shaped beads. Elliott found that this is not the case; the motor cells in the adult human cord are arranged in long nuclear masses which are not segmentally determined but have conspicuous functional relationships. For example, the long medial mass in the cervical and lumbar regions serves the sacrospinalis and other trunk muscles, while the lateral masses serve the arms and legs.

The motoneuron does not have the simple reflex connections that neurologists show in diagrams of spinal reflex arcs. Sherrington conceived of a "motoneurone pool" in the spinal gray matter into which motor tracts and reflex arcs discharged. From the histologic standpoint this takes in a group of ventral horn cells and the many small internuncial neurons clustered about them. Most motor tracts from above, discharging on the internuncial cells, make a reflex arc of more than three neurons. Lloyd,[3] at the Rockefeller Institute, has applied micro-oscillographic leads to various areas of the spinal gray matter, and by physiologic analysis of the electroneurograms has been able to show that the pyramidal tract plays on these internuncial neurons in at least three regions of the gray matter. He has also been able to distinguish [4] between the discharges of large and of small myelinated fibers and between the discharges of reflex arcs made up of only two neurons and those made up of several neurons. The simple two neuron arc consists of a large fiber from a muscle which connects directly with a ventral horn cell. These arcs mediate

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1. Denny-Brown, D.: Selected Writings of Sir Charles Sherrington, New York, Paul B. Hoeber, Inc., 1940.

2. Elliott, H. C.: Am. J. Anat. **70**:95, 1942.

3. Lloyd, D. P. C.: J. Neurophysiol. **4**:525, 1941.

4. Lloyd, D. P. C.: J. Neurophysiol. (*a*) **6**:111 and 143, 1943; (*b*) **6**:293 and 317, 1943.

myotatic reflexes. Moreover, reflex activity over extensor two neuron arcs is inhibited by the action of the multineuron arcs. In some experiments the activity of the internuncial neurons was suspended by pyramidal tract discharges. This suggests that the mechanism for reciprocal innervation may lie in the premotoneuron internuncial system. McCouch [5] supports such a hypothesis by finding that in spinal reflexes the locus of inhibition seems to be in the internuncial neurons. Thus the experimenters with this intricate electrophysiologic technic are slowly piecing together the puzzle; when the picture is complete the physiologist will be able to understand motor facilitation, inhibition and reciprocal movement. The clinician may have a better understanding of flaccid paralysis, spasm, incoordination, clonus and tremor.

Paul Weiss [6] has for several years been working on the mechanics of nerve growth in the zoologic laboratories of the University of Chicago. This subject is well summarized in the third growth symposium,[6] and references are there given to his detailed work in various biologic journals. The important point is that recent experiments on living nerve tissue, beginning with those of Harrison [7] and ending with those of Weiss, have shown that the former theories of neurobiotaxis and chemotaxis do not hold; axons do not grow out to reach their appropriate end organ because of some mysterious humor that attracts them thereto. The peripheral end of the growing or regenerating axon sends off large numbers of fine protoplasmic filaments. A few of these find their way to the muscle (if it is a motor nerve), and after functional connection is established the other, unsuccessful filaments degenerate. Just what chemical reaction causes this phenomenon is not known, but similar reactions are known in other biologic processes. In the case of the axon that is regenerating after injury, the task of the many wandering filaments is to find the old pathway to the distant muscle. This path lies in the nerve sheaths left empty when the axons degenerated. Some of the axons find these old tubes and grow down into them simply because it is the path of least resistance. The process is determined by numerical chance and mechanical advantage. In his most recent work, stimulated by the war, Weiss [8] has developed new methods of nerve splicing and nerve grafting. Sutureless splicing can be accomplished by joining the ends of the severed nerve in a sleeve of fresh or frozen and dried artery,[9] thus guiding the axons to the proper channel. Also pieces of nerve can be frozen and dried and stored for later use as nerve grafts.

Young,[10] in the department of zoology at Oxford, has also been working on the process of regeneration in nerve and muscle. He summarized his work in a paper at the last meeting of the American Neurological Association. His experiments complement those of Weiss. He has shown that in surgical union of nerves containing large and small fibers the diameter of the regenerating fibers depends on the volume of the protoplasmic nerve outgrowths ("axoplasm") and on the size of the tubes in the peripheral stump into which they flow. Motor branches of a mixed nerve regenerate larger fibers than the sensory branches. It is important to have the receiving tubes of the stump large enough to receive the motor filaments; so the suture must not be delayed too long lest the peripheral stump atrophy and shrink, and if a graft is used a nerve must be chosen with large enough tubes.

5. McCouch, G. P.; Hughes, J., and Stewart, W. B.: J. Neurophysiol. **4**:547, 1941.
6. Weiss, P.: Growth (supp.) **5**:163, 1941.
7. Harrison, R. G.: Proc. Roy. Soc., London s.B **118**:155, 1935.
8. Weiss, P.: Tr. Am. Neurol. A., 1943, to be published.
9. Weiss, P., and Davis, H.: J. Neurophysiol. **6**:269, 1943.
10. Young, J. Z.: Tr. Am. Neurol. A., 1943, to be published.

Size is important also, because no function returns until the fibers gain an adequate diameter. This takes thirty-seven days in the nearest part of the peripheral stump in a rabbit. In man the process is probably slower; so there is considerable delay in the start of regeneration, even under the best conditions. Once started, the functionally complete regeneration advances at the rate of 2.6 mm. per day. In man the rate is variable; the old estimate of 1 mm. per day is probably too slow. Fibers arriving at unatrophied muscle innervate the old end plates immediately; if regeneration is delayed the old end plates atrophy and new ones must be made. This is a slow process, and if regeneration of the nerve is too long delayed the atrophied muscle may never completely recover.

MUSCLE AND MYONEURAL JUNCTION

Carey [11] has been studying muscle and motor end plates. His investigations into the morphology and mechanics of the cross striations of skeletal muscle seem to finally get rid of the "sarcomere," which he considers "a morphological myth which has existed in the literature for over 100 years." Molecular pressure waves in the minute tubular structure of the muscle seem to be responsible for the different appearances seen; physical and chemical conditions, varying with function, therefore determine the appearance of the "striations." The variations in structure seen in degenerating muscles are structural not in the histologic but in the biochemical sense. Carey's work on the end plates [12] is of even more importance for understanding the physiology and pathology of the motoneuron. He has observed that the motor nerve plates in skeletal muscle enlarge when the muscle is stimulated to great activity; often they spread out to twice their normal size. Moreover, they change rapidly as the muscle works, expanding as the muscle contracts and retracting as it relaxes. The increase in surface area of the plate may favor the transmission of the nerve impulse to the muscle substance by increase of the surface area of the plate. The retracted motor nerve plates are related to muscle fibers with coarse, widely spaced striations; the expanded plates are related to fine, closely spaced cross striations. These structural changes suggest the correctness of the chemical theory of the transmission of the nerve impulse.

Fulton and Nachmansohn [13] have developed a new concept of the transmission of the nerve impulse, in axons as well as across synapses and across the myoneural junction (end plate to sarcoplasm). The "electrical" and "chemical" theories of transmission are conciliated by showing that acetylcholine can be metabolized at as high a rate as is required by the assumption that it is a transmitter of nerve impulses known to pass the myoneural junction in a few milliseconds. Actually it was the enzyme choline esterase with which Nachmansohn worked, and he showed in some remarkable experiments on the electric organs of fishes and the giant axons of squids that the concentration of choline esterase is sufficiently high to indicate that acetylcholine is formed and metabolizes at a rate sufficiently rapid to propagate an impulse along axons at a rate compatible with observed nerve transmisson. Moreover, the acetylcholine metabolism is intrinsically connected with the electrical discharge, there being found a close parallelism between the voltage of the action potentials and the concentration of choline esterase.

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11. Carey, E. J.; Zeit, W., and Massopust, L.: Am. J. Anat. **70**:119, 1942; Wave Mechanics in Striated Muscle: Effects of Experimental Variations in Temperature and of Microcapillarity on Cross Striations in Muscle, Arch. Path. **30**:1041 (Nov.) 1940.

12. Carey, E. J.: Am. J. Path. **18**:237, 1942.

13. Fulton, J. F., and Nachmansohn, D.: Science **97**:569, 1943.

All these new observations bring the physiologist nearer to an understanding of the contraction of muscle, which Fenn [14] has vigorously described in his monograph:

> Unlike other cells, however, the muscle cell can be conveniently stimulated to contraction, thereby bringing about an almost instantaneous transformation of its shape and its cytology, its mechanical and electrical state, its temperature, chemical composition and rate of respiration. Thus at the desire of the experimenter a whole series of new chemical reactions can be thrown into activity in an orderly and reproducible manner. This sudden transformation so produced may be properly described as an explosion. The muscle is a self-cocking explosive machine with a convenient trigger. The explosion turns chemical potential energy into mechanical energy. Thus the machine is useful. We can use it to heave rocks, sew on buttons, or for the still more delicate task of dissecting another muscle from the leg of a fly. It has a highly orderly structure of both microscopic and sub-microscopic dimensions. Many refined optical methods are available for the examination of this structure and the changes incident to the contraction. The forces developed in a muscle "explosion" are of amazing magnitude. Some of our tendons transmit forces of the order of half a ton. Single fibers of the muscle can also be isolated in Ringer's solution by painstaking dissection, and the resulting threads of muscle contract vigorously for days and exert relatively large forces.

The great enigma, however, remains unsolved: How is the chemical energy transformed into mechanical energy?

RELATION TO THE PROBLEMS OF POLIOMYELITIS

It is obvious that all phenomena of the motoneuron, myoneural junction and muscle are important for the understanding of infantile paralysis (poliomyelitis). Within the last two years the "Kenny treatment" [15] for acute and chronic poliomyelitis has become famous. It was at first empiric, but it is now based on a concept of pathology and dysfunction quite at variance with the orthodox understanding of the process. The adherents of the Kenny theory consider that infantile paralysis does harm by "spasm" of the affected muscles, not by flaccid paralysis. The antagonistic muscles are said to show "alienation" and unless retrained may permanently lose function. Other muscles are said to show "incoordination." Treatment is directed especially at the muscles in "spasm," because allowing the spastic state to continue is supposed to cause the paralysis. Some physicians have accepted the "Kenny concept" to a greater or less extent. Kabat and Knapp [16] have studied the "muscle spasm" in acute poliomyelitis and explain it as a release phenomenon, caused by lesions of the internuncial neurons in the spinal gray matter, with sparing of the ventral horn cells. They do not, however, explain what is released to cause the spasm. They seem to imply that the ventral horn cell itself is set free from its connecting neurons and thus goes into excessive activity—an unheard-of sort of neurophysiologic activity, because motor nerve cells need something to set them off; they are units depending on reflex stimulation and if left alone do not go on discharging. They also overlook the possibility that the lesions of the gray matter and meninges may act on the motor nerve cells and their axons as direct irritants, causing acute stimulation for a time. Perhaps the simple two neuron arcs of Lloyd [4b] are released when the internuncial neurons are injured, but this mechanism at best would produce a very slight postural contraction of the muscle. The main thesis of Kabat and Knapp's paper is that prostigmine causes relaxation of the muscle spasms of poliomyelitis and makes for more rapid recovery.

14. Fenn, W. O.: Muscle, in Cattell, J.: Biological Symposia, Lancaster, Pa., Jaques Cattell Press, 1941, vol. 3, p. 2.

15. Pohl, J. F., and Kenny, E.: Kenny Concept of Infantile Paralysis and Its Treatment, Minneapolis, Bruce Publishing Co., 1943.

16. Kabat, H., and Knapp, M. E.: The Use of Prostigmine in the Treatment of Poliomyelitis, J. A. M. A. **122**:989 (Aug. 7) 1943.

Their data on this point are certainly suggestive, but with the many variables in recovery rate and the fact that hot foments were also used, they seem hardly justified in stating that "the drug significantly increased the range of passive motion, decreased or eliminated deformities in some instances by relaxation of hypertonus and in some cases improved active motion." [16] Just how the postigmine might act to give these results is not clear. In all probability the use of prostigmine can be looked on as a method of setting free more acetylcholine by inhibiting choline esterase. One would expect this to increase the function over the remaining reflex arcs, rather than diminish it.

At the New York Neurological Institute spasm of muscles and degeneration were studied by Moldaver [17] in 49 cases of poliomyelitis. He used the electrical methods of measuring chronaxia and making electromyograms. He controverts quite flatly the Kenny findings. Using objective methods, he has found that "muscle spasm" does not lead to neuromuscular degeneration and that the antagonists of the involved muscles, the "alienated muscles," have lost power because of damage to the motoneuron in the cord. The "incoordination," if found at all, is not what neurologists recognize under that name, but the effect of partial paralysis.

Watkins, Brazier and Schwab,[18] working independently and using different but equally sound objective electrophysiologic methods, also disagree with the "Kenny concept" of the pathologic process in poliomyelitis. They summarize their findings by saying:

1. In poliomyelitis the term "muscle spasm" is inadequate to describe the complexity of dysfunction which is revealed by electromyography.

2. In the acute stage, only muscles with some degree of paralysis discharge electrical potentials at rest; these electrical abnormalities are not correlated with the presence of clinical "spasm."

3. Partially paralyzed muscles are hyperirritable to passive stretching as indicated by electrical discharges and pain; the muscle tension thus developed appears to be a reflex protective mechanism.

4. The electrical activity in paretic muscles at rest increases during the period of improving motor power, and the pattern of discharges corresponds with that seen in muscles during regeneration of peripheral nerves. When improvement in motor power ceases, spontaneous electrical discharges disappear.

5. No abnormal electrical activity is associated with the muscle contractures of the late stage of poliomyelitis, nor are any discharges present in completely paralyzed muscles.

6. The concept of "mental alienation" does not contribute to the explanation of paresis in our cases, since objective signs of a disease process were always present in the paretic antagonists of muscles in "spasm."

7. Increase of voltage of action potentials during successive ergographic tests is an index of recovery of motor power.

8. Of the three concepts of Kenny, the only one upheld by our objective measurements is that of "incoordination," although the term is misleading. We demonstrated not only simultaneous activation of protagonists and antagonists, but also intermittent synchrony of individual discharges from opposing muscles, such as is found in peripheral nerve injuries during regeneration of axons. Disordered reciprocal innervation seems to be a more descriptive term for this type of dysfunction.

Thus it is being demonstrated once more in the history of medicine that new and empiric methods of treatment, backed by uncritical enthusiasm, may produce many cures but much physiologic nonsense. The treatment may be good, but the ex post facto rationalizations of the therapeutist are usually bad.

17. Moldaver, J.: Physiopathologic Aspect of the Disorders of Muscles in Infantile Paralysis, J. A. M. A. **123**:74 (Sept. 11) 1943.

18. Watkins, A.; Brazier, M. A. B., and Schwab, R. S.: Concept of Muscle Dysfunction in Poliomyelitis, Based on Electromyographic Studies, J. A. M. A. **123**:188 (Sept. 25) 1943.

MYASTHENIA GRAVIS

It has been known for years that the thymus gland is hyperplastic or neoplastic in about half the cases of myasthenia gravis. Irradiation with roentgen rays was tried some years ago, but the therapeutic effect was found to be variable. In a few cases there was improvement; in the majority there was none. Not until the last eight years had thoracic surgery advanced to a point where operative removal of the thymus might be tried. Blalock and his colleagues [19] at first removed a cystic tumor from the thymus with relief of myasthenia and then turned their attention to operation on thymic glands that showed no disease by clinical or roentgenographic examination. Six patients were treated by removal of all surgically available thymus tissue. In 5 of these the tissue was considered hyperplastic. Three of the patients have shown continued improvement in their myasthenic symptoms.

These results should not be considered discouraging if they are compared with the early work on removal of the thyroid and the parathyroids. Roentgen irradiation was tried in this field and found wanting because of the unpredictability of the results. Surgical removal was at first moderately successful and is now satisfactory. With myasthenia gravis it may well be that the disappointing cases are those in which thymic tissue not only lies in the substernal region but has spread into less surgically accessible areas. Patients whose cases suggested this have been operated on by Cope at the Massachusetts General Hospital.[20]

Viets has been carrying on a systematic study of myasthenia gravis from the medical and neurologic standpoints. By running a special outpatient clinic, he has kept a large group of these relatively rare patients, and has been able to make many observations. With Schwab [21] he has worked out a diagnostic test by the use of prostigmine. A dose of 1.5 mg. of prostigmine methylsulfate with 0.6 mg. of atropine sulfate is given intramuscularly. Examination of muscular function is made thereafter every ten minutes for an hour. The presence and the amount of improvement in muscular strength are a great aid in making the diagnosis. One must be careful not to give the drug in cases of progressive muscular atrophy and amyotrophic lateral sclerosis, in which bulbar palsy might be precipitated with fatal results. They have found [22] that pregnancy generally causes an improvement in symptoms. Strickroot and his associates [23] report a case in which a mother with the disease gave birth to a myasthenic child. This is the first case reported, as far as I know, of direct inheritance of the disease, but it has been classified [24] among the instances of familial myopathy on the basis of the close relationship of the condition to the inheritable endocrine dyscrasias of the thymus and the thyroid. The recent surgical work just reported on makes this view more tenable, since it points to the possibility that myasthenia gravis is more a metabolic or endocrine than a neurologic disease. This concept is supported by the physiologic work of Harvey, Lilienthal and Talbot,[25] who have found electromyographic evidence that the disturbance in myasthenia is at the neuromuscular junction (motor end plates) and that the

19. Blalock, A.; Harvey, A. M.; Ford, F. R., and Lilienthal, J. L., Jr.: Treatment of Myasthenia Gravis by Removal of Thymus Gland, J. A. M. A. **117**:1529 (Nov. 1) 1941. Blalock, A.; Mason, M. F.; Morgan, H. J., and Riven, S. S.: Ann. Surg. **110**:544, 1939.

20. Cope, O.: Personal communication to the author.

21 Schwab, R. S., and Viets, H. R.: New England J. Med. **219**:226, 1938.

22. Viets, H. R.; Schwab, R. S., and Brazier, M. A. B.: Effect of Pregnancy on Course of Myasthenia Gravis, J. A. M. A. **119**:236 (May 16) 1942.

23. Strickroot, F. L.; Schaeffer, R. L., and Bergo, H. L.: Myasthenia Gravis Occurring in Infant Born of Myasthenic Mother, J. A. M. A. **120**:1207 (Dec. 12) 1942.

24. Aring, C., and Cobb, S.: Medicine **14**:77, 1935.

25. Harvey, A. M.; Lilienthal, J. L., Jr., and Talbot, S. A.: Bull Johns Hopkins Hosp. **69**:547, 1941.

disorder resembles that caused by curare. It could result from a deficiency in acetylcholine or an increase in the stimulation threshold of the end plates. Ayer [26] and Reese [27] have written comprehensive reviews of this subject.

CONFIRMATION OF FREUDIAN THEORIES

Many leaders in the fields of medicine, psychology, anthropology and sociology would accept the statement that Freud made the greatest contribution of his time to the study of personality. In medicine the study of personality has always been recognized as important, but in the last few years it has been emerging from the age-old stage of intuition and "common sense" to a level that at last is beginning to be scientific. It is beginning to be appreciated that interpersonal relations have a direct bearing on the problems of internal medicine and surgery as well as on those of psychiatry. Three recent books mark an advance in this field: Murray's "Exploration in Personality," 1938 [28]; Rapaport's "Emotions and Memory," 1942,[29] and Sears's "Survey of Objective Studies of Psychoanalytic Concepts, 1943.[30] All three of these books attempt to bring together psychoanalysis and experimental psychology. A recent editorial in *The Journal of the American Medical Association* [31] states that "the criteria for judging freudianism as a scientific contribution must be the same as those employed in judging any other scientific discipline." With this sound pronouncement I agree. The three books mentioned all contain sections which are attempts to evaluate freudian observation and theory by nonfreudian psychologic technics. Sears's monograph is frankly devoted to this object. Murray's book [32] is the first comprehensive attempt along this line. He says: "Our work is the natural child of the deep, significant, metaphorical, provocative and questionable speculations of psychoanalysis and the precise, systematic, statistical, trivial and artificial methods of academic personology." Rapaport has investigated an important phase of repression.

The report [30] by the Social Science Research Council on Psychoanalytic Concepts is timely and important. It was prepared by Robert R. Sears, Professor of Child Psychology at the University of Iowa, for the Council's Committee on Social Adjustment. It is a book of 156 pages devoted to the appraisal of freudian theory by means of objective investigation, both observational and experimental (some by psychoanalysts, but much by investigators trained in other schools). As yet there have been only a few attempts to apply the experimental method. Some, however, are significant, and, as already suggested, every one interested in the field should agree that the freudian concepts must be tested by other than psychoanalytic methods before the theory can be accepted as fact. A start is being made in this direction.

The theory of repression is probably the most fundamental of Freud's concepts. Rapaport's book could be roughly described as an "investigation of repression," but this would be unfair, because he is careful to show that words must be exactly defined and fields delineated before a project is begun. He summarizes by saying [29]:

> Originally our problem was posed by the fact that in the taking of case-histories, clinical psychologists and psychiatrists and other medical men frequently find that the patient "forgets" to give what is obviously the most pertinent information, or unwittingly gives false replies

26. Ayer, J. B.: New England J. Med. **228**:422, 1943.
27. Reese, H. H.; Lewis, N. D. C., and Sevringhaus, E. L.: 1942 Year Book of Neurology, Psychiatry and Endocrinology, Chicago, Year Book Publishers, Inc., 1943.
28. Murray, H. A.: Exploration in Personality, New York, Oxford University Press, 1938.
29. Rapaport, D.: Emotions and Memory, Baltimore, Williams & Wilkins Company, 1942.
30. Sears, R. R.: Survey of Objective Studies of Psychoanalytic Concepts, Bulletin 51, Committee on Social Adjustment, New York, Social Science Research Council, 1942.
31. Psychoanalysis and the Scientific Method, editorial, J. A. M. A. **122**:811 (July 17) 1943.
32. Previously reviewed (Arch. Neurol. & Psychiat. **44**:1152 [Dec.] 1940).

to crucial questions. These peculiar phenomena of "forgetting," as well as the generalized amnesias to which it was considered intimately related, were conceived and designated as being of an "emotional origin." Our task was to investigate whether and in what sense this is generally maintained, and what the basis of the assertion is.

The task comprised reviewing a large mass of literature and performing many special tests. The conclusion is that the processes of perception, memory and forgetting are closely connected with emotional feelings. The problem grew larger as the work proceeded, and why a person remembers certain events, why attention and interest are heightened, appears closely related to why one represses and forgets other events. Freud's theory is substantiated, but the problem is found to be wider; "emotions and memory" are found to encompass a large part of thinking.

The essence of Freud's idea of repression lies in the elimination from consciousness of all ideas or memories that might help to reactivate a painful anxiety. In addition to this primal sort of repression there is an associative amnesia; i. e., many memories entirely unrelated in content can be repressed simply because they had a time relation with the anxiety reaction created by parental punishment of strongly motivated behavior. Since sex behavior in children is one of the most consistently punished forms of action in Western civilization, sex is one of the most frequent sources of repression. By such a mechanism Freud explains the amnesia for most of the experiences of preschool years.

It is well known that an amnesia something like that postulated in the theory of repression can be induced by hypnosis. The phenomena of posthypnotic suggestion in which a person performs some foolish act some time after awakening from the hypnotic state and has no idea why he does the act certainly show that mental processes can be made subconscious and can continue to act at that level. No experiments, however, seem to throw much light on repression itself and whether anxiety and unpleasantness are factors in its induction. Such data as there are suggest that unpleasantness interferes with memory. The theory that amnesia for events occurring before the age of 5 years is due to repression is controverted by some investigations [33] which show clearly that learning functions in infants are not well developed; the memorizing process is poor at this age and parallels the poor recall for infantile experiences.

The libido theory postulates that all drives to emotional relations with others are, broadly speaking, sexual in origin. In short, love and hate of all types are libidinal. Few persons would doubt the validity of the generalization after contemplating the differences between the bull and the ox. The theory carries with it, however, the corollary that the infant must have libido at birth and that sexual behavior must begin in earliest infancy. It was this idea of infantile sexuality which brought down on Freud's head the greatest storm of criticism. This is easily explained by the cultural attitude toward sex in Europe thirty years ago. Since then observations on infants and nursery school children have recorded "such a tremendous number of instances of behavior organized around oral, anal, urethral and genital functions and ideas that Freud may be freed forevermore of any charge of overestimating the frequency of such behavior." [20] Nevertheless it must be remembered that Freud did not work with children; he got his data largely from psychoneurotic adults who recalled and reported to him their childhood behavior. These clinical data were slowly amassed and eventually led to the description of infantile libidinal development as first oral, then anal and urethral and finally genital. Malinowski's [34] work, however, shows that genital play occurs very early in certain savage tribes among whom it is not repressed.

33. Child, I. L.: J. Abnorm. Psychol. **35**:453, 1940.
34. Malinowski, B.: Psychoanal. Rev. **14**:20, 1927.

Worry over sex differences, fear of losing the penis by boys ("castration complex") and a desire to have a penis among girls ("penis envy") are also psychoanalytic observations considered important in determining later behavior. These phenomena certainly occur, but Freud's belief that they were practically universal has not been backed up by any subsequent work. Few psychiatrists doubt that the complex has affected certain neurotic adults, and many child psychologists have seen obvious examples of the fear in children from 2 to 5 years old, especially those that have been subjected to surgical treatment. Nevertheless no data are given in the psychoanalytic literature that show how often the fear occurs in anxious children or in normal children. Conn [35] made an attempt with "play technic" to find out how often children are emotionally upset by learning about the sex difference between boys and girls, and found evidence that about 8 per cent were disturbed by the problem. Surveys of adult sex behavior, however, have shown that adequate early sex instruction is correlated with adequate orgasm in women; poorly instructed women are more likely to be frigid. What is needed is many more data from direct observation of children. Only from such observations can answers be given to the questions: When and how shall I instruct my child about sexual differences? Is "fear of castration" in boys universal, common or rare? Is it universal, common or rare for girls to envy boys their male genital development? There is plenty of evidence that these questions are important in neurotic developments. Whether or not they are of importance to sociology and anthropology is for future work to decide. At present it looks as if Freud's postulates were too broad and should be applied only to "Western European culture" and perhaps only to neurotic persons in that culture.

Freud's clinical observations that sexual perversions arise from mixed and opposing impulses and are commonly multiple are strongly corroborated by others.[36] Perversions are much more common than is usually believed, and they are usually related to lack of orgasmal adequacy. The pervert, then, is not "hypersexed" in the ordinary sense; it seems that he is often obsessed with sex (and thereby overactive in that line) because of lack of normal satisfaction. A large number of persons with perverted impulses recall childhood satisfactions from the anal, urethral and oral zones. This gives some substantiation to the psychoanalytic theory that excessive preoccupation with stimulation of these zones before the development of genital sexuality may predispose a child to later development of perversion.

Quite different from the simpler anal satisfactions and interests common to most infants and many adults is the "anal eroticism" recognized by freudians. This consists in pleasure arising from stimulation of the rectal mucous membrane due to retained feces. There is also pleasure when the retained mass is expelled, stretching and stimulating the rectum. A complex theory has arisen about this form of pleasure, that it leads to the "anal character," the cardinal attributes of which are orderliness, stinginess and obstinacy. Sears points out that some psychologic investigations show that these traits tend to go together but that there is no evidence, except the psychoanalytic observations on neurotic patients, that show the relationship of these character traits to the "anal erotic" syndrome. Sadism is said to be related to the anal character, but surveys by nonpsychoanalytic methods indicate that masochism is almost as common. It is probable, then, that Freud's statements about the polymorphism of perversity are correct and that patients with anal interests form a neurotic group, but there is no good confirmatory

35. Conn, J. H.: Am. J. Orthopsychiat. **10**:747, 1940.

36. Terman, L. M.: Psychological Factors in Marital Happiness, New York, McGraw-Hill Book Company, Inc., 1938. Sears.[30]

evidence that orderly, stingy and obstinate people are either "anal erotic" or sadistic. Two surveys by psychologists indicate that paranoid patients have a much higher incidence of homosexuality than other psychotic groups. Also there are clinical data indicating that alcoholism may often be related to homosexual trends. Both of these observations support findings of Freud. It is obvious that there is need now for more good observation of children's eliminative and sexual habits with follow-up for years, to prove or disprove the freudian theories.

The direction in which a person discharges his love and hate is certainly of great importance. As a child he directs it toward other persons; later, toward more abstract objects. This choice of the object for emotional discharge has been called "cathexis" by Freud (taking the electrical term because of its value as a simile). The theory of cathexis does not need confirmation, because it is a redefinition of a phenomenon which is accepted as common knowledge. The subordinate phenomena can be examined critically.

The sequence of events in the choice of love objects is of prime importance in psychoanalytic theory. It is briefly as follows: The first genital sexuality is homoerotic; the child explores himself and is interested in himself. Observation of infants amply corroborates this simple sort of "narcissism." Love is also turned toward the mother because of her nursing and tending activities. Between 6 and 8 years of age the child inhibits this direct mother attachment, and the "latency period" sets in and goes on until he is 10 or 12 years of age, when puberty brings on heterosexual interests. The "oedipus situation" is deep attachment of a boy for his mother (which is inhibited because of fear of the father); there is a less well defined situation in the love of a daughter for the father. Workers in psychiatry and psychology using other than freudian methods have amply confirmed the occurrence of this sequence of events in many cases. There is, however, no proof that it is typical or the rule. In fact, anthropologists [36] have evidence that in primitive races genital development begins early and goes on steadily through adolescence, showing no signs of a latency period and no oedipus situation. Certain psychologic surveys, notably that of Bell [37] on midwestern children in the United States, corroborate the existence of a latency period in "Western civilization," whereas others reviewed by Sears do not find evidence of it. Cathexis is a useful psychologic concept, but the pattern varies so greatly with the cultural pattern and is so bound up with the process of learning by experience that Freud's interpretation is too narrow. There is good evidence that it applies to European culture and gives a good explanation for certain types of neurosis. Homosexuality seems to be not infrequently related to a strong mother attachment.

Sears pays particular attention to "fixation" and "regression." It was observed by Freud that certain patients who had reached a normal heterosexual adjustment returned to earlier modes of satisfaction. A man might be frustrated in his attempt to adjust in an adult way to his wife and revert to a childish attempt to get mothering. This would be "regression" caused by "frustration"; "fixation" of affection on a love object is a prerequisite for such frustration. Reactions like the example given are commonly recognized; psychoanalysts consider the mechanism of regression a good explanation for much neurotic and even schizophrenic behavior. Sears's review describes much careful experimental work. He concludes:

> The success with which animal psychologists have attacked fixation and regression is dimmed somewhat by the fact that experimental regression is not entirely representative of the Freudian clinical phenomenon. There is sufficient systematic relation between them, however, to suggest that most of the experimental findings can be applied safely to the latter.

37. Bell, S.: Am. J. Psychol. **13**:325, 1902.

If fixation is defined as an unusually strong object attachment, or instrumental act, regression can be considered as the reactivation of a fixated but previously relinquished response following the weakening of a later established response. The weakening, as has been shown, can be secured through frustration by punishment, frustration by removal or reward, satisfaction or alcohol. When the ongoing response is weakened by any of these four factors, other responses become prepotent; and if the ensuing response is one that was strong at some earlier date, the change in behavior is called regression. These experimental findings give sound support to Freud's contention that regression is a function of fixation, and they suggest that his notion of the importance of frustration is correct as far as it goes but is not the only factor that can give opportunity for fixation to play its role.

This discussion of repression, libido, infantile sexuality, perversion and regression gives examples of the way in which Freud's postulates are now being examined by psychologists and psychiatrists by nonfreudian technics. One might summarize by saying that these workers have found some confirmation for the libido theory, infantile sexuality, the "castration complex," the polymorphism of perversion, and repression and regression. They have found evidence against accepting the subdivisions of infantile sexuality as characteristic of children in general, against the theory of anal eroticism and its effect on character, and against using such concepts as the "castration complex" and "penis envy" except in a limited way for certain cultural areas. Also there is good evidence against the theory of infantile repression. More work should be done along these lines, for the work sketched in the foregoing paragraphs is spotty and little of it follows a program, with the obvious exceptions of Murray's and Rapaport's monographs. One must admit that it looks as if Freud made some remarkably shrewd generalizations from his clinical observation of human nature! It is important to know which generalizations are true and which are false, and this can be determined only by future research along the lines indicated.

SHOCK THERAPY

The hopes of 1938, when insulin shock therapy was at its height, have vanished. Sound psychiatrists reviewing the situation at present show much less enthusiasm for any of the shock treatments. For example, Rennie [38] says:

The tested methods of psychiatry and psychotherapy are still important, and the most important methods available. The procedure in shock therapy, because of its hazards, belongs in the hands of thoroughly trained physicians and should be limited to hospital practice, not office or consultation routine. No convincing rationale for therapy has yet emerged. There are dangers to be encountered, to life and to the mental performance of the sufferer. These cannot be shoved aside.

The use of insulin, except as an aid for relieving certain symptomatic manifestations of schizophrenia, is largely discarded. In fact, some workers [39] have published series of cases with controls that show insulin therapy to be no better in its results than the former types of conservative hospital care. While insulin shock therapy was at its height, the use of metrazol shock came in. This type of treatment was easier to employ and had more dramatic effects. At first hopes were raised that here was a cure for schizophrenia, but they were soon disappointed when it appeared that the only patients benefited with any regularity were the ones with depressions. Metrazol, however, caused such brutal convulsions, with so many fractures and so much terror in the patients, that it never was as much used as its quick successor, electric shock. This method of treatment is now sweeping the field of therapy in neuropsychiatry, and a warning against indis-

38. Rennie, T. A. C.: Psychiatry **6**:127, 1943.

39. Gootlieb, J. S., and Huston, P. E.: Treatment of Schizophrenia: Follow-Up Results in Cases of Insulin Shock Therapy and in Control Cases, Arch. Neurol. & Psychiat. **49**:266 (Feb.) 1943.

criminate use is needed. In the hands of careful physicians the electrical shocking machines have given good results in shortening the depressions of the manic-depressive psychoses and in relieving the chronic agitated-depressive states of the involutional period. Also the outward behavior of schizophrenic patients is often changed for the better. Many data have been amassed, and a symposium on the subject was held at the last meeting of the American Psychiatric Association.[40] In general, the results in 1943 corroborate the preliminary impression given by reports in 1941.[41] Involutional melancholia is usually benefited; other depressions seem to be shortened in a majority of cases; manic states are improved in about half the patients treated, and the method is of no use for the neuroses.

Electric shock is easily given, dramatic to the family and relatively pleasant for the patient, because it leaves him with an amnesia, so that he does not mind having had the fit (unless he happens to be one of the 3 to 5 per cent that suffer a fracture or dislocation). These facts are all to the good, but the difficulty is that they play too easily into the hands of the enthusiastic therapeutist and the charlatan. Electric shock, unfortunately, is being used indiscriminately for all sorts of nervous and mental troubles, from anxiety states, which could be relieved by psychotherapy, to multiple sclerosis, for which its use is obviously a stupid counsel of despair.

Another aspect of electric shock treatment must be discussed. The anatomic and physiologic effects on the brain of electricity, currents such as those used in this therapy, are not known. The investigators do not agree,[42] and the investigations are inadequate. Since the therapeutists do not yet know what they are doing to the brain by electroshock, it certainly is only common prudence to go slowly, use as few shocks as possible and make careful examination of the patient's mental state, especially memory, before and after treatment. Such procedure is certainly followed by the careful and well trained men who use the method. The less discriminative shockers, however, do not seem to fear the possibly permanent intellectual defects that may occur from repeated electrical convulsions. In hospitals it has been found that many disturbed and active patients can be made quieter by repeated shock treatments. Their behavior is so much improved that nursing is simplified. Some of them look, however, as if they had been partially decorticated. I feel it imperative to repeat what I said in 1939[43]: "One feels doubtful of the ethical standards that allow shock treatment to be given for the purpose of making nursing easier for the hospital administration. It comes dangerously close to punishment, and logically one might ask: 'Why not euthanasia?' "

Massachusetts General Hospital.

40. Am. J. Psychiat., to be published.

41. Cobb, S.: Review of Neuropsychiatry for 1941, Arch. Int. Med. **68**:1232 (Dec.) 1941.

42. Globus, J. H.; van Harreveld, A., and Wiersma, C. A. G.: J. Neuropath. & Exper. Neurol. **2**:263, 1943. Hassin, G. B.: Cerebral Changes in Fatal Cases Following Treatment with Barbital, Soluble Barbital U. S. P., Insulin and Metrazol, Arch. Neurol. & Psychiat. **42**: 679 (Oct.) 1939.

43. Cobb, S.: Review of Neuropsychiatry for 1939, Arch. Int. Med. **64**:1328 (Dec.) 1939.

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